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Published in:
Journal of Law and the Biosciences

DOI:
[10.1093/jlb/lxx043](https://doi.org/10.1093/jlb/lxx043)

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):
Nordberg, A., Minssen, T., Holm, S. H., Horst, M., Mortensen, K., & Møller, B. L. (2018). Cutting edges and weaving threads in the gene editing ()evolution: reconciling scientific progress with legal, ethical, and social concerns. *Journal of Law and the Biosciences*, 5(1), 35-83. <https://doi.org/10.1093/jlb/lxx043>



Cutting edges and weaving threads in the gene editing (Я)evolution: reconciling scientific progress with legal, ethical, and social concerns

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ABSTRACT

Gene-editing technology, such as CRISPR/Cas9, holds great promise for the advancement of science and many useful applications technology. This foundational technology enables modification of the genetic structure of any living organisms with unprecedented precision. Yet, in order to enhance its potential for societal benefit, it is necessary to adapt rules and produce adequate regulations. This requires an interdisciplinary effort in legal thinking. Any legislative initiative needs to consider both the benefits and the problematic aspects of gene editing, from a broader societal and value-based perspective. *This paper stems from an interdisciplinary research project seeking to identify and discuss some of the most pressing legal implications of gene-editing technology and how to address these.*

While the questions raised by gene editing are global, laws and regulations are to a great extent bound by national borders. This paper presents

a European perspective, written for a global audience, and intends to contribute to the global debate. The analysis will include brief references to corresponding USA rules in order to place these European debates in the broader international context.

Our legal analysis incorporates interdisciplinary contributes concerning the scientific state of the art, philosophical thinking regarding the precautionary principle and dual-use issues as well as the importance of communication, social perception, and public debate. Focusing mainly in the main regulatory and patent law issues, we will argue that (a) general moratoriums and blank prohibitions do a disservice to science and innovation; (b) it is crucial to carefully consider a complex body of international and European fundamental rights norms applicable to gene editing; (c) these require further developments grounded in consistent and coherent implementation and interpretation; (d) legal development should follow a critical contextual approach capable of integrating interdisciplinary contributions and broad multilevel societal dialog.

KEYWORDS: gene editing, CRISPR/Cas9, patents, regulation, interdisciplinary perspectives, ELSI

I. INTRODUCTION

In April 2015, Chinese scientists announced the use of gene-editing technology in human embryos.¹ Chinese laws and regulations did not explicitly control or monitor research concerning modification of the germline of humans.² Reportedly, the embryos used were unviable and not intended to be implanted. The announcement sparked controversy, igniting strong reactions in the scientific community, and fueled public debate concerning the regulation of gene-editing technology. This highlighted once more that it is more pressing than ever to debate and make national and international decisions on how to interpret, adapt, or produce adequate rules and regulations. Given the complexity and the great variety of applications of the technology, this calls for an interdisciplinary effort and the incorporation of interdisciplinarity in legal thinking.

This paper is the result of an interdisciplinary research project conducted by a European group of lawyers, biologists, philosophers, social scientists, and physicists. Taking into account the international context, we identify and debate some of the perceived legal and regulatory challenges that scientists, legislators, and society as a whole face in Europe.

We argue that before society can harness this technology's potential it is imperative to consider from a broader societal and value-based perspective not only the enormous benefits that gene editing may bring, but also its problematic aspects. Our legal analysis incorporates contextual elements, based on a legal reflection built upon interdisciplinary contributes such as the scientific state of the art, philosophical analysis concerning the precautionary principle and the dual-use problem, the importance of communication, social perception, and public debate.

While the questions raised by gene editing are global, laws and rules are to a great extent bound by national borders. The present piece is an European perspective

¹ Puping Liang et al., *CRISPR/Cas9-Mediated Gene Editing in Human Triprenuclear Zygotes*, 6 *PROTEIN & CELL* 363–72 (2015).

² Yaojin Peng, *The Morality and Ethics Governing CRISPR–Cas9 Patents in China*, 34 *NAT. BIOTECHNOL.* 616–18 (2016).

written for a global audience, intended as a research contribute to the global debate on how to regulate the potential uses and applications of gene-editing technology. The analysis will include brief references to corresponding USA rules in order to place these European debates in the broader international context.

Gene-editing technology, such as CRISPR/Cas9,³ holds the potential to guide seminal discoveries within basic science and open a Pandora's box of practical applications. This foundational technology provides tools that enable researchers with a basic knowledge of biochemistry and molecular biology to modify with improved precision the genetic structure of any living organism. Possible applications include plant, microbial, animal, and human genetic intervention.

In plant biology, CRISPR/Cas9 technology represents a precise and timewise unprecedented efficient tool for gene editing and an economically feasible route to engineered plant variants with desired characteristics, such as improved nutritive value or disease resistance, high content of health-promoting compounds, or offering more efficient starting material for production of biofuels or high value compounds. Light-driven production systems based on engineered photosynthetic cells and using carbon dioxide as the sole carbon source offer the opportunity to facilitate the move toward a biobased society.⁴ In the microbial field, improvement of existing fermentation-based platforms and development of entire new ones is envisioned for production of bulk and fine chemicals including bioethanol, jet fuels,⁵ natural sweeteners,⁶ and health-promoting antioxidants such as resveratrol.⁷

Within the animal area, development of sterile male malaria mosquitoes⁸ and new gene-drive technology⁹ provide new, effective tools in the fight against malaria. Gene editing can be used to combat schistosomiasis and other snail-borne diseases,¹⁰ and to increase growth rate and body mass in animal and poultry husbandry, as well as in aquaculture.

In humans, this technology may form the basis for new approaches to eradicating or preventing severe genetic diseases such as Huntington's disease, sickle cell anemia, and many other illnesses. In theory, it could equally be used in humans in order to modify, introduce, or improve traits, features, and performance levels.

³ CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. Cas9 stands for CRISPR-associated protein 9.

⁴ *Plant Power—The Ultimate Way to Go Green: Birger Lindberg Møller at TEDxCopenhagen 2012*, YouTube (2017), <https://www.youtube.com/watch?v=6oiWJOTydWAa> (last accessed Apr. 27, 2017); Lærke Münter Lassen et al., *Redirecting Photosynthetic Electron Flow into Light-Driven Synthesis of Alternative Products Including High-Value Bioactive Natural Compounds*, 3 ACS SYNTH. BIOL. 1–12 (2014).

⁵ Pauli Kallio et al., *Renewable Jet Fuel*, 26 CURR. OPIN. BIOTECHNOL. 50–5 (2014).

⁶ Varanuj Chatsudthipong & Chatchai Muanprasat, *Stevioside and Related Compounds: Therapeutic Benefits Beyond Sweetness*, 121 PHARMACOL. & THER. 41–54 (2009); Recombinant Production of Steviol Glycosides, PCT/US2011/038967. 02.06.2011.; Kim Olsson et al., *Microbial Production of Next-Generation Stevia Sweeteners*, 15 MICROB. CELL FACT. 207 (2016).

⁷ Marta G. Novelle et al., *Resveratrol Supplementation: Where Are We Now and Where Should We Go?* 21 AGEING RES. REV. 1–15 (2015).

⁸ James E Gentile, Samuel Rund & Gregory R Madey, *Modelling Sterile Insect Technique to Control the Population of Anopheles gambiae*, 14 MALARIA J. 92 (2015).

⁹ Andrew Hammond et al., *A CRISPR-Cas9 Gene Drive System Targeting Female Reproduction in the Malaria Mosquito Vector Anopheles gambiae*, 34 NAT. BIOTECHNOL. 78–83 (2015).

¹⁰ Sara Reardon, *Welcome to the CRISPR Zoo*, 531 NATURE 160–63 (2016).

However, before harnessing the potential of gene-editing technology society has to address broad and complex ethical and societal challenges. Potential uses of gene-editing technology that are particularly controversial include changes in the human germline passed on to future generations; human enhancement; genetic modification of wild insect and other animal populations; and modified crop plants for use as human food and livestock fodder.

Around the globe, scientists, small and large-scale industries, interest organizations, artists, and policy makers are engaging in a vigorous and value-laden debate. Literature and cinematographic works fuel fears and high hopes. The mass media contribute to construction of extremist narratives concerning emerging technology. Major industrial players are portrayed as focusing on short-term economic gain, being over optimistic on benefits, blind to possible negative effects, and with little interest in engaging in an open debate with other relevant stakeholders. Popular culture is rife with alarmism, misperceptions, and dystopian futuristic scenarios that find their way into the policy debate via the discourse of the technology's opponents. On the other side of the spectrum, we find hyperoptimistic views of possibilities and minimization of risks communicated by proponents of immediate and unlimited use of the technology.

In between these radical positions, scientists worry over the possibility of a negative public perception toward GMOs resulting in a spillover effect into synthetic biology and genetic editing. This is partly due to the very nature of gene-editing technology, which makes it particularly difficult to establish distinctions and clear boundaries in both scientific terms and in the eyes of the public. Issues of traceability, containment, and distinctions between natural and 'unnatural' also challenge previous definitions, regulatory frameworks, and case law.¹¹

Controversies abound and legal battles are inevitable. Examples can be found in ongoing patent litigation and patentability debates, as well as in calls for technological moratoria and research limitation. In 2011, a group of non-governmental organizations released a report with specific regulatory recommendations on new biological techniques for building and remaking organisms for research and commercial uses ranging from medicines to biofuels. Synthetic biology is described as 'an extreme form of genetic engineering' and a moratorium on its use was advocated.¹² Recent applications in plant sciences to produce vanillin in yeast carried out at the University of Copenhagen¹³ stimulated a fierce international debate concerning both the well-being of indigenous vanilla farmers and labeling the vanillin produced as *natural*.¹⁴ As for gene editing in humans, the aforementioned announcement of gene editing in unviable

¹¹ *Gene Editing in Legal Limbo in Europe*, 542 NATURE 392, 392 (2017).

¹² The International Civil Society Working Group on Synthetic Biology, *The Potential Impacts of Synthetic Biology on the Conservation & Sustainable Use of Biodiversity: A Submission to the Convention on Biological Diversity's Subsidiary Body on Scientific, Technical & Technological Advice*, (2011), http://www.etcgroup.org/sites/www.etcgroup.org/files/publication/pdf_file/cbdsynbiocsosubm.pdf (last accessed May 10, 2015).

¹³ Nethaji J. Gallage et al., *Vanillin Formation From Ferulic Acid in Vanilla planifolia is Catalysed by a Single Enzyme*, 5 NAT. COMM. 4037 (2014). Esben H. Hansen et al., *De Novo Biosynthesis of Vanillin in Fission Yeast (Schizosaccharomyces pombe) and Baker's Yeast (Saccharomyces cerevisiae)*, 75 APPL. & ENVIRON. MICROBIOL. 2765–74 (2009).

¹⁴ § 6 (2) Biotech Directive. Cf. Gina Kolata, *A Proposal to Modify Plants Gives GMO Debate New Life*, THE NEW YORK TIMES, 2017, http://www.nytimes.com/2015/05/29/a-proposal-to-modify-plants-gives-gmo-debate-new-life.html?_r=0 (last accessed June 5, 2015).

embryos¹⁵ prompted a torrent of criticism, fueled fears of a eugenic future, and reignited the human enhancement debate. Two distinct groups of high-profile scientists called for a moratorium on editing germline genomes with CRISPR/Cas9 and zinc-finger nucleases.¹⁶

Editing of the human germline is prohibited in several jurisdictions and heavily regulated in others.¹⁷ In the EU, the patentability of such technology is also subject to restrictions under the Biotechnology Directive.¹⁸ Recently, in the USA a *National Academies Report* concluded that 'heritable germline genome editing trials must be approached with caution, but caution does not mean they must be prohibited'.¹⁹ Given the potential for life-saving treatment, cost-effective manufacture of pharmacological substances, and sustainability gains, current approaches should be revisited and debated in light of legal, ethical, social, and life science arguments.

These anecdotes illustrate very clearly how new applications of gene editing present several complex, multifaceted challenges, to both the scientific and medical communities, in addition to political decision makers and indeed to society as a whole. Against that complex background, this paper provides an European interdisciplinary perspective on the challenges, threats, and opportunities associated with gene editing. Debates on regulating emerging technology risks becoming excessively polarized and often focusing more on the technologies potential, dystopic or utopic uses, rather than on its actual scientific reality. In Section II, this paper will begin with a scientific preface presenting the current scientific state of the art and its limitations and available technology. This section will also address the perceived regulatory and ethical hurdles faced by scientists. Ethical interrogations are often central to public policy choices in life science innovation. Section III presents two central ethical issues often present in public policy arguments concerning the regulation of gene editing technology: dual-use issues and the precautionary principle. These have also been recurrent topics in European debates concerning emerging technology. Incorporating the previous analysis, Section IV proceeds to the core of this paper a legal analysis and interpretation of existing laws and regulations applicable to gene editing. Two aspects are considered: first international, European, and EU human rights law establishing fundamental principles and as we argue constituting an umbrella framework for regulation and second the regulatory role

¹⁵ See Puping Liang et al., *CRISPR/Cas9-Mediated Gene Editing in Human Trippronuclear Zygotes*, 6 *PROTEIN & CELL* 363–72 (2015); Xiangjin Kang et al., *Introducing Precise Genetic Modifications into Human 3PN Embryos by CRISPR/Cas-Mediated Genome Editing*, 33 *J. ASSIST. REPROD. & GENET.* 581–88 (2016).

¹⁶ Edward Lanphier et al., *Don't Edit the Human Germ Line*, 519 *NATURE* 410–11 (2015); David Baltimore et al., *A Prudent Path Forward for Genomic Engineering and Germline Gene Modification*, 348 *SCIENCE* 36–38 (2015).

¹⁷ As for Europe, see for example the restriction imposed by article 13, Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (CETS n.º 164), [hereinafter Oviedo Convention], entered into force on Dec. 1, 1999. Only 28 countries have ratified (out of 47 member states). Absences include, eg the EU as an institution, Germany, Ireland, Italy, The Netherlands, Poland, Sweden, UK, Israel, and the Russian federation.

¹⁸ See with further references: Timo Minssen & Ana Nordberg, *The Impact of 'Broccoli II' and 'Tomatoes II' on European Patents in Conventional Breeding, GMOs, and Synthetic Biology: The Grand Finale of a Juicy Patents Tale?* 34 *BIOTECHNOL. L. REP.* 81–98 (2015); cf. Ana Nordberg & Timo Minssen, *A 'Ray of Hope' for European Stem Cell Patents or 'Out of the Smog into the Fog'? An Analysis of Recent European Case Law and How it Compares to the US*, 47 *IIC – INT'L REV. INTEL. PROP. & COMPETITION L.* 138–77 (2016).

¹⁹ NATIONAL ACADEMY OF SCIENCE AND NATIONAL ACADEMY OF MEDICINE, *REPORT: HUMAN GENOME EDITING: SCIENCE, ETHICS, AND GOVERNANCE* 145 (The National Academies Press 2017).

exercised by patent. Although patent norms were not developed with the main purpose of regulating technology, these have a de facto regulatory role. In particular in Europe, where exceptions to patentability are directly linked and based in a legislative logic of inserting public policy mechanisms in patent law. Furthermore, in the quest to provide a balanced level of incentive to innovation and technologic development *case-law* development on patentability and patent eligibility rules and requirements contains an element of public policy capable of influencing science and technology development. Likewise, patent ownership disputes create narratives and current of public opinion, which find their way into the political discourse. The *patent wars* for the CRISPR-CAs9 invention will be analysed from a legal view point in Section IV, and also from a public communication perspective in Section V. In this section, we debate the pitfalls and necessary considerations involved in public communication of the technology to support robust sociotechnical development. The final sections of this paper will use these arguments and debates as a background for discussion and suggestions as to how to proceed (Section VI) and our final remarks (Section VII).

II. SCIENCE AND TECHNOLOGY

The interlinked global challenges related to climate change, population increase, migration, food insecurity, environmental degradation, depletion of fossil fuels, economic inequality, and financial vulnerability are well known and their impacts documented. It is necessary to develop disruptive innovative approaches offering new industries a clear competitive edge in the global market. Successful transition to and realization of a knowledge-based bioeconomy relies heavily upon the ability to turn these challenges into vehicles for sustainable growth, and is dependent on increased focus on interdisciplinary research addressing the global challenges that humanity is facing and providing science-based solutions to alleviate problems envisioned. Researchers and industries need to collaborate in developing new and innovative products from renewable resources and novel green technology that possess transformative power, that are within the economic realm, and that benefit consumers. In parallel, health care systems face the urgent challenge of newly arising infectious diseases and growing lifestyle-based diseases. Development of new antibiotics, effective and non-toxic treatments of cancers, and personal medicines tailored to the individual genetic profile will gain impact. In this realm, the availability of technology-enabling targeted and efficient genome editing offers numerous opportunities.

II.A. The State of the Art

In microbes and plants, a brute force type of genome editing has been available to obtain genetic variation based on radiation or chemical mutagenesis. These procedures introduce changes in the DNA of organisms. Changes may range from single mutations in a few or multiple genes to multiple mutations in numerous genes to deletion of entire segments of DNA, or to major DNA relocations and rearrangements within the genome of the organism. In all cases, the changes in DNA introduced by the irradiation and chemical mutagenesis approaches occur at random positions in the host genome. The effort to select a specific single mutant which has gained a desired property among the large collection of mutants obtained is time consuming and labor intensive. In addition, to gain the full benefit of an identified desired mutation, a series

of back-crosses to the wild-type organism are required to remove other simultaneously introduced mutations with negative effects. Nevertheless, these procedures have been important because they have enabled introduction of changes that would not be achievable by classic crossings between related species or between a high yielding species and a wild relative. The parallel development of molecular-based high-throughput screens such as TILLING (Targeting Induced Local Lesions in Genomes) has made it easier to identify mutations in a specific gene.²⁰

Initial brute force approaches have been superseded by more efficient targeted mutagenesis approaches. Within recent decades, researchers including microbiologists, plant biologists, and human biologists have made major progress using the tools of molecular biology to refine methods of gene editing. The main objective has been to introduce a desired mutation in a specific gene in a selected genome without simultaneous introduction of numerous side mutations. These series of approaches developed have been dependent on sequence-specific nucleases such as meganucleases, zinc-finger nucleases, and TAL effector nucleases.²¹ These nucleases contain a modular DNA-binding domain engineered to recognize the specific target DNA sequence as well as a nuclease domain cleaving the target DNA. Although outperforming the classic non-targeted mutagenesis approaches, these methodologies were not straightforward to apply, being based on construction of large proteins, and suffered from context-dependent lack of specificity. However, these pioneering studies have spurred continued efforts to develop simpler and more rapid gene-editing systems with improved target specificity. The most recent result of these efforts is the CRISPR/Cas9 system.¹⁶ In this gene-editing system, the Cas9 endonuclease is targeted to a specific location in the genome guided by a short-guide RNA sequence derived from the CRISPR array and a second helper RNA. These RNAs may be fused into a single RNA molecule.²² This mode of recognition greatly simplifies system design. A recent publication by Barrangou and Horvath²³ provides an overview of the development of the CRISPR-Cas technology over the last decade. Videos illustrating the key steps in CRISPR/Cas-based gene editing are available on the internet.²⁴

In nature, the CRISPR/Cas9 system is part of a memory-based immune defense system found throughout the kingdom of prokaryotes including bacteria and archaeal species enabling them to counteract infection from viruses.²⁵ Different types of systems

²⁰ Cecilia K. Blomstedt et al., *A Combined Biochemical Screen and TILLING Approach Identifies Mutations in Sorghum bicolor L. Moench Resulting in Acyanogenic Forage Production*, 10 PLANT BIOTECHNOL. J. 54–66 (2011).

²¹ Patrick D. Hsu, Eric S. Lander & Feng Zhang, *Development and Applications of CRISPR-Cas9 for Genome Engineering*, 157 CELL 1262–78 (2014); Khaoula Belhaj et al., *Editing Plant Genomes with CRISPR/Cas9*, 32 CURR. OPIN. BIOTECHNOL. 76–84 (2015); Samuel H. Sternberg et al., *Adaptation in CRISPR-Cas Systems*, 61 MOL. CELL 797–808 (2016); Matthias Heidenreich & Feng Zhang, *Applications of CRISPR–Cas Systems in Neuroscience*, 17 NAT. REV. NEUROSCI. 36–44 (2015).

²² Martin Jinek et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCIENCE 816–21 (2012).

²³ Rodolphe Barrangou & Philippe Horvath, *A Decade of Discovery: CRISPR Functions and Applications*, 2 NAT. MICROBIOL. 17092 (2017).

²⁴ See for example <https://www.youtube.com/watch?v=MrpcBvIrpig> (last accessed Sept. 12, 2017).

²⁵ Marie-Laurence Lemay, Philippe Horvath & Sylvain Moineau, *The CRISPR-Cas App Goes Viral*, 37 CURR. OPIN. MICROBIOL. 103–09 (2017).

are known.²⁶ A CRISPR locus typically harbors a number of CRISPR-associated genes (Cas genes) encoding endonucleases as well as the CRISPR signature domain composed of a series of direct repeat sequences interspaced with short spacer sequences derived from viral genomes. When a virus species attacks a bacterium or archaea, the Cas endonuclease dissects a small piece of the viral DNA and integrates this piece of DNA at a specific position in the DNA of the prokaryote designated as the CRISPR sequence array. The CRISPR sequence array is thus composed of a series of variable viral spacer sequences each separated by direct repeats and orchestrated by the endonuclease activity of the Cas enzyme. Upon each new viral attack, a new spacer derived from the virus genome sequence is integrated into the CRISPR sequence array. The region of the viral genome from which the spacer is derived is designated the protospacer and is characterized by possessing an adjacent motif which serves to direct the Cas9 endonuclease to cleave the viral DNA. If the protospacer adjacent motif is mutated, virus resistance is lost.

The CRISPR signature sequence is transcribed as a single RNA and then processed by different pathways into shorter RNAs each harboring individual viral spacer sequences. In the Cas9 system, hybridization to an additional non-coding transactivating RNA is required to direct the Cas9 endoproteinase to recognize and specifically degrade the complementary sequences present in the infecting virus. A virus is not able to successfully infect bacteria or archaea which carry a signature CRISPR sequence corresponding to a sequence in the viral genomes.

The CRISPR/Cas9 system can be transferred to eukaryotic cells including mammalian cells and has been redesigned to facilitate targeted gene editing in eukaryotes. From the description above, it is apparent that the CRISPR/Cas9 system requires three components: the Cas9 endonuclease, a non-coding transactivating RNA, and mature CRISPR RNA. To facilitate the experimental protocols for gene editing using the CRISPR/Cas9 system, the two RNAs may be combined into a single-guide RNA.²⁷ For gene editing of a eukaryotic organism, the mature CRISPR RNA sequence may now be substituted with a short sequence derived from the target gene. Multiple guide RNA sequences may be used to target several genes in the same transformation event or to target other effectors, eg transcription factors to alter gene expression.²⁸ In case a gene encoding an inactive Cas9 nuclease is introduced, a wide array of modifications of gene regulation in the host cell may be introduced in a partly programmable manner.²⁹

With this CRISPR/Cas9 technology, the DNA of the host organism is cut at a site in the genome predefined by its sequence. At this location, a single base mutation, gene deletions, replacement of a mutated disease-causing gene, insertion of a different isoform of the gene from the same species or new genes from different organisms may be introduced. In contrast to classic mutation breeding, by using CRISPR/Cas9

²⁶ Tomáš Čermák et al. *A Multipurpose Toolkit to Enable Advanced Genome Engineering in Plants*, 29 PLANT & CELL 1196–217 (2017).

²⁷ Jinek et al., *supra* note 22, at 816–21.

²⁸ Čermák et al., *supra* note 26; J. A. Aznar-Moreno & T. P. Durrett, *Simultaneous Targeting of Multiple Gene Homologs to Alter Seed Oil Production in Camelina sativa*, 58 PLANT CELL PHYSIOL. 1260–7 (2017).

²⁹ Antonia A. Dominguez, Wendell A. Lim & Lei S. Qi, *Beyond Editing: Repurposing CRISPR–Cas9 for Precision Genome Regulation and Interrogation*, 17 NAT. REV. MOL. CELL BIOL. 5–15 (2015).

technology the site at which the mutation is introduced may be controlled upfront and the type of mutation introduced may also be designed.³⁰

The Cas9 encoding gene is of bacterial origin and does not occur naturally in plants and animals including humans. When the desired change in the DNA of the host organism has been accomplished using CRISPR/Cas9 methodology, the gene encoding the Cas9 enzyme may be completely removed. Following genome editing, sequencing of the entire genome can be carried out to ascertain that the changes introduced are as originally planned and that no other changes have resulted during the process. This requires sequencing of the genome before and after editing. Genome sequencing technology is constantly being improved, and within the next decade such a quality check will be feasible economically as well as timewise.³¹ When CRISPR/Cas9 gene-editing technology is being used to insert a gene from a foreign organism into a host cell, the resulting organism should be considered as genetically engineered and subject to the regulations for genetically engineered organisms. When CRISPR/Cas9 technology is used to introduce mutations to correct a malfunctioning gene in the host organism and the CRISPR/Cas9 gene cassette is subsequently removed, no foreign genes have been inserted. Proponents of CRISPR/Cas9 technology would therefore argue that the resulting organism is not classified as genetically engineered because the same mutation could have been obtained by classic mutagenesis-based breeding.³²

Proponents of newer and much more precise gene-editing technology would argue that the organisms obtained would constitute no additional challenges to the environment in comparison to those already present in nature. However, the impact of genome editing is determined by the nature of the specific trait being modified or introduced. Microorganisms subjected to gene editing and grown on an industrial scale in environmentally contained fermenters would not give rise to descendants in nature as long as unintended spillage is avoided. Gene-edited crop plants would be grown in the fields, and traits introduced would be transferred to descendants and to cross-pollinating-related species. In humans, traits introduced in egg cells would transfer to subsequent generations. Thorough risk analyses are thus required in spite of benefits envisioned related to improved bioproduction in yeast or photosynthetic cells, more robust crop plants, or elimination of serious genetically inherited human diseases from a family. In other cases, non-awareness of the type of associated risks demands thorough risk analysis.

Recent technological developments within gene editing open up new opportunities in all branches of life science. The use of CRISPR/Cas9 in synthetic biology approaches offers the opportunity to design systems with new desired properties spanning from in vitro systems and cell factories to microorganisms, plants and animals including humans. It is also important that the CRISPR/Cas9 system affords functional analysis of a selected gene in its natural environment. In basic science, this offers a unique approach to assigning functions to specific genes and regulatory elements. The importance of

³⁰ Xuan Liu et al., *Application of CRISPR/Cas9 in Plant Biology*, 7 ACTA PHARM. SIN. B 292–302 (2017); C.C.M. van de Wiel et al., *New Traits in Crops Produced by Genome Editing Techniques Based on Deletions*, 11 PLANT BIOTECHNOL. REP. 1–8 (2017).

³¹ Armin Scheben et al., *Towards CRISPR/Cas Crops—Bringing Together Genomics and Genome Editing*, NEW PHYTOL. (2017) doi: 10.1111/nph.14702.

³² *Id.*

precise gene editing relates to the fact that the genomes of eukaryotic organisms contain tens of millions of DNA bases the sequence of which encodes several thousand genes. The ability to knock out the function of a specific gene, to replace a mutated gene, or to insert a new gene at a desired position in the genome has been a major challenge. CRISPR/Cas9 technology offers precise editing of genetic modules and controlling elements. It offers new opportunities to edit, modulate, or interrupt the function of genes in their endogenous environment of most organisms. In basic science, this offers a new approach for functional characterization of genes.³³

Previously, molecular technology for therapeutic treatment of genetic disorders in humans has not been available due to unacceptable risks. CRISPR/Cas9 offers the opportunity to simultaneously perturb several genes enabling studies of additive effects of polygenetic disorders in humans and thus offers an opportunity to cure polygenic diseases. Diseases caused by 'loss-of-function genes' as is the case in cystic fibrosis and sickle-cell anemia could be cured.

In plants, the CRISPR/Cas9 system offers the possibility to exchange a specific malfunctioning gene or a disease-causing mutation with a wild-type gene. Such homologous recombination only occurs at very low frequency (<1%) using classic genetic engineering. Increased resistance to pests, improved tolerance to drought, flooding, and saline soils may offer higher yields in parallel with increased plasticity and adaptation to environmental stresses based on optimized content of specialized metabolites. The breeding of more robust plants that provide stable and high yields in spite of adverse growth conditions exacerbated by climate change is a major global challenge which must be dealt with to avoid a global shortage of food.³⁴

II.B. Open Questions and Scientific Challenges

CRISPR/Cas9 technology clearly represents a major advantage with respect to gene editing of microorganisms, plants, and animals including mammals. The technology is a key tool for scientists who want to study biological systems at the molecular level offering quick access to knockout mutants, site-specific mutations, and transfer of genes between organisms that cannot be crossed. But, like any technology, CRISPR/Cas9 technology also has its limits. It is not 100% specific, meaning that DNA sequences outside the planned target site may be cleaved by Cas9 endonuclease. In other situations, the target sequence may bind to Cas9 without being cleaved, which in most cases will cause an altered gene expression pattern.³⁵ Whole genome control sequencing will reveal information about off-target cleavage of genes but cannot be used to monitor changes in expression pattern.³⁶ One uncertainty related to current reports on successful gene editing using the CRISPR/Cas9 system in plants is the stable heritability of the trait introduced.³⁷ The editing process requires introduction of the gene encoding Cas9 endonuclease and guide RNA with a sequence complementary to the DNA sequence of the target gene. If the CRISPR/Cas9 construct is not removed, it is

³³ Holger Puchta, *Applying CRISPR/Cas for Genome Engineering in Plants: the Best is Yet to Come*, 36 CURR. OPIN. PLANT BIOL. 1–8 (2017).

³⁴ Puchta, *supra* note 33, at 1–8; Agustin Zsögön et al., *Genome Editing As a Tool to Achieve the Crop Ideotype and De Novo Domestication of Wild Relatives: Case Study in Tomato*, 256 PLANT SCI. 120–30 (2017).

³⁵ Dominguez et al., *supra* note 29.

³⁶ Scheben et al., *supra* note 31.

³⁷ Jinek et al., *supra* note 22, at 816–21.

difficult to determine whether the genetic change introduced was indeed inherited by the next generation or whether the mutation was produced once again. The presence of the CRISPR/Cas9 construct for several generations would also be expected to increase the risk of off-target changes. Strategies for insulating the CRISPR/Cas9 construct are available but far from always used.³⁸ In microorganisms and plants, off-target mutations introduced by CRISPR/Cas9 technology may be eliminated by back-crossings.

Lack of 100% specificity is obviously of major concern regarding use of the technology in human clinical applications introducing permanent changes in the genome and offspring, although most off-target aberrations may not have any importance. In this context, it is important to remember that, on average, each human receives approximately 60 new mutations in their genome from the parents.³⁹ Some of these mutations constitute a positive driving force in evolution, while others may be neutral or disabling.

The rapid adoption of CRISPR/Cas9 technology by the global research community and companies is based on the relative ease of this procedure compared to previous protocols for gene editing and the improved set of molecular biology tools available. Open-source guidelines and easy access to constructs, e.g. from Addgene,⁴⁰ further speed up implementation of the CRISPR/Cas9 system in a range of different microorganisms, plants, and animals including mammals. The speed of implementation is a challenge to attempts to achieve a balanced discussion of the positive and negative aspects of this potent gene-editing technology. Likewise, with the easy and largely open distribution of gene constructs and molecular kits, the scientific community, legal authorities, and individual researchers have few opportunities to prevent individuals or groups of people from engaging in uses of gene constructs and protocols without prior regulatory approval. Such experimentation may take place in multiple private settings. Citizen-scientists, researchers, and well-established DIY communities share the responsibility to use technology responsibly.

II.C. Communication, Ethics, and Law in the Lab

In public opinion, issues of multidrug-resistant microbes are often considered coupled with and arising from the introduction of genetically engineered plants harboring genes conferring antibiotic resistance. From a scientific perspective, this association is not correct. However, it demonstrates the great challenge and social responsibility borne by the research community to communicate and engage in upfront discussion. Some researchers would argue that changes in biological food chains and in microbial, plant, and wild animal communities caused by climate change are of far more importance and impact than those caused by introduction of genetically engineered species.⁴¹ Although

³⁸ *Id.*; Xiuhua Gao et al., *An Effective Strategy for Reliably Isolating Heritable and Cas9 -Free Arabidopsis Mutants Generated by CRISPR/Cas9-Mediated Genome Editing*, 171 *PLANT PHYSIOL.* 1794–800 (2016); Eszter Kapusi et al., *Heritable Genomic Fragment Deletions and Small Indels in the Putative ENGase Gene Induced by CRISPR/Cas9 in Barley*, 8 *FRONT. PLANT SCI.* 540 (2017); Yanfei Mao, Jose Ramon Botella & Jian-Kang Zhu, *Heritability of Targeted Gene Modifications Induced by Plant-Optimized CRISPR Systems*, 74 *CELL MOL. LIFE SCI.* 1075–93 (2017).

³⁹ Reed A. Cartwright et al., *A Family-Based Probabilistic Method for Capturing De Novo Mutations from High-Throughput Short-Read Sequencing Data*, 11 *STAT. APPL. GENET. & MOL. BIOL.* 1544–6115, 1713 (2012).

⁴⁰ See Addgene.org (2017), <https://www.addgene.org> (last accessed May 17, 2017).

⁴¹ See United States Environmental Protection Agency (2017), https://19january2017snapshot.epa.gov/climatechange_.html (last accessed May 17, 2017).

this is correct, public mistrust toward implementation of new technology needs to be addressed through serious studies and monitoring, but not by delaying use of promising technology and our efforts to move toward a biobased society that would mitigate some of the negative effects of climate change. The recent open letter signed by 110 Nobel Prize winners regarding genetically engineered Golden Rice does not embrace or invite opponents of the technology to have a say. In the debate about gene editing, an argument often presented by natural scientists is that ‘it is the end product which matters’.⁴² All the evidence suggests that this is not the way to discuss the issue, for it is crucial to take into account the concerns of stakeholders and the general public in setting policy priorities.

Different applications generate diverse risks and benefits. It is important to base assessments on a clear scientific understanding of different production systems, their related benefits, and disadvantages, incorporating ethical reasoning in methodologies. At a time when humanity needs to move toward a biobased society, it is more than ever important that the methodologies behind biological production are understood and their implementation in terms of producing medicinal compounds, flavors, and other food ingredients is adequately debated upfront. These discussions need to be based on inputs from all stakeholders, thus including the general public, politicians, industry, and scientists from a broad range of fields and disciplines. From a life science scientist perspective, it seems clear that challenges need to be taken seriously and properly addressed in order to ensure that production systems are optimized with respect to overall reduced risks, minimized environmental impact, and commercial viability. Such public policy debates require engaging multiple stakeholders and the interdisciplinary academic community. Only through close interdisciplinary dialog and broad societal involvement, we can achieve the vital development of a sound legal policy at the service of the global community.

III. ETHICAL PERSPECTIVES ON REGULATION AND UNCERTAINTIES

The recent development of CRISPR/Cas9 as a superior tool for genome editing in plants, animals, and humans raises profound ethical issues and poses challenging questions to stakeholders including scientists and regulators. In this section, we will reflect on some of the ethical issues that have become pressing in the context of research using CRISPR/Cas9 technology and some of its potential applications. To begin with, it will be useful to distinguish two lines of ethical discussion regarding gene editing. On the one hand, one might discuss whether scientists should even be allowed to make changes to living systems at the genetic level. The very idea of genetically engineering naturally evolved life may seem morally abhorrent, whatever benefits we envisage to come out of it. This is not the ethical outlook that we will adopt in this paper. On another approach, presented in this paper, the central question is not whether the technology is intrinsically morally wrong, but how to use it in a morally justified way. Under what conditions should using it be allowed? What sort of applications might it be used to develop? What regulatory initiatives should be taken? In other words, CRISPR/Cas9 is a

⁴² Detlef Weigel, *The End Product is What Matters* (2016), <https://www.mpg.de/10444274/genome-editing-breeding-better-crops> (last accessed May 17, 2017); Felix Wolter & Holger Puchta, *Knocking Out Consumer Concerns and Regulator's Rules: Efficient Use of CRISPR/Cas Ribonucleoprotein Complexes for Genome Editing in Cereals*, 18 *GENOME BIOL.* 43 (2017).

tool that may be used in many different contexts, by many different people, for many different purposes. And it is fast becoming a stalemate of genetics research everywhere. Therefore, one thorny issue concerns how to regulate the use of CRISPR/cas9 (and future gene-editing technology) given the fundamental uncertainty about the possible consequences of having this tool in our hands. In this section, we will comment on two themes concerning decision making about the use of gene editing. First, we will discuss whether a precautionary approach to gene editing should guide regulation. Second, we consider the dual-use aspect of gene-editing technology. An underlying debate, which has received considerable attention, concerns the possibility of the gene editing of humans (and human embryos) for scientific, therapeutic, and enhancement purposes. This debate involves profound questions about specific applications of the technology and about the very distinction between therapy and enhancement.⁴³ However, in the context of this paper, we limit ourselves to considering how to make decisions about such specific applications of the technology.

III.A. Precaution

The advent of CRISPR/Cas9 technology makes it pertinent to consider how to reach the right decisions about what to do in terms of regulating, funding, and developing the technology and the research and applications that it may enable. Whatever specific application of CRISPR/Cas9 one might envisage, important questions are likely to arise about possible risks to human health and the environment. As with many other fields of technology, there will also be issues concerning social justice. Who will benefit from use of the technology? Matters of security will also loom large. A tool such as CRISPR/Cas9 could be used for nefarious purposes, and we have to consider this when regulating its use. Finally, an important issue concerns who has the authority to make decisions about what changes can be made to which organisms using gene-editing technology. Is it morally permissible or perhaps required for one generation of humans to make changes to the genetic profile of their descendants through germline genetic therapy or enhancement, or both?

The current debate about the ethics of gene editing was set off by the use of the CRISPR/Cas9 technology on human embryos. The ensuing suggestion to establish a moratorium on some uses of CRISPR/Cas9 is an example of taking a precautionary approach to a certain domain of application of the technology. This is arguably justified by the fact that the consequences of going ahead remain highly uncertain. While it is generally agreed that the consequences of the arrival of CRISPR/Cas9 are unclear, there is less consensus on how to regulate its use and development. Should it be permitted to use CRISPR/Cas9 on viable but discarded human embryos to study questions about

⁴³ On the legal concept of enhancement, see Nordberg *infra* note 148; on the difficulties of establishing and using such distinction in legal practice, see Ana Nordberg, *Human Enhancement from Ethical Interrogations to Legal (Un)certainty*, in *INTELLECTUAL PROPERTY PERSPECTIVES ON THE REGULATION OF NEW TECHNOLOGIES* (Tana Pistorius ed., 2018).

human development,⁴⁴ or to develop gene therapy and/or enhancement?⁴⁵ Should we use CRISPR/Cas9 technology to make cows without horns and engineer mosquitoes to resist the parasite that causes malaria? Progress in genetics and fine-tuning gene-editing techniques will only raise more questions like this. What is certain is that decisions must be made in situations characterized by uncertainty. When uncertainty meets biotechnology, there is often pressure on decision makers to invoke the Precautionary Principle.

A relatively clear and representative formulation of the *Precautionary Principle* is this:

The Precautionary Principle asserts that parties should take measures to protect public health and the environment, even in the absence of clear, scientific evidence of harm. It provides for two conditions. First, in the face of scientific uncertainties, parties should refrain from actions that might harm the environment, and, second, that the burden of proof for assuring the safety of an action falls on those who propose it.⁴⁶

The Precautionary Principle has gained traction during the last 50 years.⁴⁷ It is invoked in the Kyoto Protocol,⁴⁸ while the European Union allows countries to invoke the Precautionary Principle when making decisions about a risky activity.⁴⁹ Debate about the use of CRISPR/cas9 in some domain or other is likely to revolve around questions about whether a precautionary approach should inform regulation. In the debate about GMOs, many European countries have enacted restrictions on genetically modified crops and food on the basis of the 'Precautionary Principle'.⁵⁰ Influential organizations such as Greenpeace, Friends of the Earth, and ETC group consistently cite the *Precautionary Principle* as a justification for strict regulation or moratoria on development and use of biotechnology. The principle also governs international legal arrangements such as the United Nations Biosafety Protocol.⁵¹

Given its status as an enabling technology and its wide range of applications, we find that there is no single question about whether gene editing per se should be allowed or banned. Nevertheless, making decisions about the use of gene editing on a case-to-case basis will still amount to making decisions about the regulation of a technology that

⁴⁴ Haroon Siddique, *British Researchers Get Green Light to Genetically Modify Human Embryos*. THE GUARDIAN (2017), <https://www.theguardian.com/science/2016/feb/01/human-embryo-genetic-modify-regulator-green-light-research> (last accessed May 8, 2017).

⁴⁵ Brendan P. Foht, *Gene Editing: New Technology, Old Moral Questions*, THE NEW ATLANTIS (2016), <http://www.thenewatlantis.com/publications/gene-editing-new-technology-old-moral-questions> (last accessed May 8, 2017).

⁴⁶ Ken Geiser, *Establishing a General Duty of Precaution in Environmental Protection Policies in the United States: A proposal*, in PROTECTING PUBLIC HEALTH AND THE ENVIRONMENT: IMPLEMENTING THE PRECAUTIONARY PRINCIPLE (Carolyn Raffensperger & Joel Tickner eds., 1999).

⁴⁷ For a series of examples supposed to show why absence of scientific certainty should not be required for precaution, see PAUL HARREMOES ET AL. (EDS), THE PRECAUTIONARY PRINCIPLE IN THE 20TH CENTURY: LATE LESSONS FROM EARLY WARNINGS (2002).

⁴⁸ Kyoto Protocol to the United Nations Framework Convention on Climate Change, FCCC/CP/L.7/Add.1, Kyoto (1997).

⁴⁹ European Commission (2000). *Communication from the Commission on the Precautionary Principle*. <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:52000DC0001> (last accessed May 21, 2017).

⁵⁰ Andrew Porterfield, *Is the Precautionary Principle Guiding Law or a Political Notion?*, GENETIC LITERACY PROJECT (2016), <https://www.geneticliteracyproject.org/2016/06/23/precautionary-principle-guiding-law-political-notion/> (last accessed May 21, 2017).

⁵¹ Geiser, *supra* note 46.

comes with the possibility of significant and perhaps very great harm to humans and the environment. This seems to support applying the Precautionary Principle and significantly restricting the use of gene editing. However, there are important reasons to be critical of the Precautionary Principle as a guide to making decisions under conditions of uncertainty. Consider the time when genetic engineering was in its infancy and researchers were beginning to develop recombinant DNA methods. In a letter published by a group of experts in *Science*⁵² in the wake of a meeting organized by the National Academy of Sciences in the USA, the authors recommended a moratorium on *all research* on recombinant DNA studies on the basis of the possibility that there *might* be risks. The famous *Asilomar conference* followed the year after, focusing on what sort of recombinant DNA research could be safely undertaken. Commenting on the precautionary approach initially taken to recombinant DNA, Watson suggests that that approach may have been morally misguided: ‘There were desperately sick people out there, people with cancer or cystic fibrosis—what gave us the right to deny them perhaps their only hope?’⁵³

What Watson is criticizing here is neglect of the costs of *not* doing something despite the risks of doing it. In its most simple formulation, the *Precautionary Principle* may seem to ignore the costs of not continuing a line of research and development. We find that while a broadly precautionary approach to regulation of gene editing is justified, it is important that the *Precautionary Principle* is interpreted in a way that avoids a disproportionate (and potentially incoherent) focus on the possible harm. According to the analysis we favor, a precautionary approach should be guided by an understanding of the *Precautionary Principle* along the lines suggested by Steel.⁵⁴ In this account precautions will not be justified if they are as likely to lead to harm of the same or bigger magnitude as the activity with respect to which they are proposed.⁵⁵ We thus suggest an alternative to traditional cost–benefit analysis. Whether or not to adopt cost–benefit analysis in situations of uncertainty is a complex question. Moreover, assessing this question in any detail is beyond the scope of this paper. However, a significant worry should be noted about cost–benefit analysis, namely that it ‘requires an ability to make quantitative predictions of the costs and benefits of alternative policy options’.⁵⁶ This in turn suggests that cost–benefit analysis may in situations of scientific uncertainty ‘lead to an inability to decide whether the benefits of a regulation would be greater or less than the costs’.⁵⁷

III.B. The Dual-Use Problem

A technology may be characterized as a dual-use technology when it can be used for both *good* and *bad* purposes.⁵⁸ It is characteristic of dual-use technology that the risk

⁵² Paul Berg et al., *Potential Biohazards of Recombinant DNA Molecules*, 185 *SCIENCE* 303, 303 (1974).

⁵³ JAMES D. WATSON, *DNA: THE SECRET OF LIFE* 98 (2013).

⁵⁴ DANIEL STEEL, *PHILOSOPHY AND THE PRECAUTIONARY PRINCIPLE: SCIENCE, EVIDENCE, AND ENVIRONMENTAL POLICY* (2014).

⁵⁵ *Id.* chapter 2.

⁵⁶ *Id.* at 23.

⁵⁷ *Id.* at 23.

⁵⁸ For an in-depth discussion of the dual use dilemma, see Seumas Miller & Michael J. Selgelid, *Ethical and Philosophical Consideration of the Dual-use Dilemma in the Biological Sciences*, 13 *SCI. & ENG. ETHICS* 523–80 (2007).

is sufficiently high that it can be used in bad ways. Furthermore, dual-use technology tends to generate a problem because increasing the possibility of production of benefits will tend to increase the possibility of misuses of the technology. Thus, dual use of a technology gives rise to questions about how to make decisions about regulating the development and use of dual-use technology. Gene editing is arguably a dual-use technology. The features that make it powerful, such as the possibility of making highly targeted changes to genomes, is the reason why it holds great promise, but also why it raises great concerns.

The dual-use aspect of gene editing means that it raises a series of ethically significant decisions that ‘revolve around balancing scientific freedom, governance, risk and security’.⁵⁹ These decisions will confront not just national governments but also individual scientists, who must decide what research to conduct and to publish; research institutions, which must decide, among other considerations, how to regulate research within their confines, how to educate their researchers, and what laboratory security measures should be in place; funding organizations, which must decide how considerations of dual-use research and technology are incorporated in their application and review processes; professional societies, which must make decisions about the development, promulgation, and/or enforcement of codes of conduct and education; editors and publishers, who must make decisions on review and publication of potentially dangerous papers; and international organizations, which must make decisions concerning relevant global policy.⁶⁰

Summing up, CRISPR/Cas9 and future gene-editing technology can potentially produce enormous benefits to humans, but the uncertainty about possible harm that may result from large-scale gene editing means that a precautionary approach is advisable to policy decisions that respect a proportionality constraint on acceptable precautions. Furthermore, the dual-use nature of gene editing entails that a range of initiatives should be considered concerning its application. These include research oversight mechanisms, policies for funding agencies, policies for journal publishers, institutional and professional codes of conduct and ethics, and awareness-raising and educational initiatives for a range of audiences.

III.C. Law and Ethics in Emerging Technologies

Law and morality constitute two separate, but intersecting normative systems. The sphere of personal and group beliefs, conceptions, and feelings on what constitutes *good* or *bad* conducts is necessarily broader than the sphere of state enforced mandatory conducts. Law requires normative decisions balancing, and sometimes choosing between different ethical perspectives. Understanding the need to include ethical thinking in legal development efforts, in the following section we analyse existing norms, their possible interpretation(s), and applicability to gene-editing technology. The topics here debated will be revisited and inform the analysis of the human rights framework (Section IV.A), specific regulations (Section IV.B), and public policy norms in patent law with regulatory effect (Section IV.C).

⁵⁹ FILIPPA LENTZOS, DUAL USE IN BIOLOGY AND BIOMEDICINE 14 (2015).

⁶⁰ *Id.*

IV. LAW AND GENE EDITING

Regulation of emerging technology can be pursued through norms in different fields of law either directly or indirectly. The same is also valid as far as gene editing is concerned. This section focuses on two types of interrelated legal issues with practical implications for the future direction and development of the technology. *First*, we will consider selected questions concerning regulation of the technology in its strict sense, i.e. establishing rules concerning to what extent, how, by whom, and under what conditions gene editing should be allowed. In this sense, this section considers the underlying legal framework based on international and European fundamental rights, and also examines specific examples of rules and regulations. *Second*, we will examine issues of patentability of gene editing and the current disputes on ownership of the CRISPR-CAS9 technology.

As we will argue, both these questions are interconnected and have broader practical repercussions beyond legal theoretical debates. Patent law has an indirect regulatory effect and is in this sense connected with regulatory efforts as such. Being a type of incentive and reward structure, patent law's intended function is to provide well-balanced incentives and rewards to ensure that investment in innovation is sufficiently attractive so that a steady flow of beneficial new products and processes are developed and made available to society. In this sense, the application of an exception from patentability denies the benefit of that incentive to a specific invention. However, patent eligibility norms also carry a broader symbolic regulatory effect, which extends the reach of refusal of a patent grant beyond the invention examined and even beyond the patent system. For example, a refusal to grant on morality grounds might result in a chain reaction of overall reduction in the various types of incentives to innovate and invest in the areas of research concerned.

The application of such norms to gene-editing patent applications is a *de facto* powerful policy tool. Moreover, patent ownership disputes can also have a chilling effect on investment and delay market introduction of socially beneficial innovations. Due to the importance of the technology and the potential 'blockage effect' of ongoing patent litigation, alternative private law mechanisms are emerging, and will here be considered. These are intended to minimize such effects and allow the use and further development of the technology regardless of the outcome of *patent wars*.

IV.A. Human Rights: an Umbrella Framework for Regulation

International treaties and conventions generate obligations for signatory states as to their reception and integration in the corresponding national legal orders. National law must respect and be applied in a manner consistent with those obligations. In this sense, human rights norms provide guidance and serve as platforms for harmonization of national legislative and adjudicative developments and form the basis of an international umbrella framework for regulation. *The United Nations Educational, Scientific and Cultural Organization* (UNESCO) has issued three declarations relevant to genetic technology.

The *Universal Declaration on the Human Genome and Human Rights*⁶¹ declared the human genome as a symbolic ‘heritage of humanity’.⁶² Article 24 mandates UNESCO’s International Bioethics Committee (IBC) to ‘give advice concerning the follow-up of this Declaration, in particular regarding the identification of practices that could be contrary to human dignity, such as germ-line interventions’.⁶³ It does not as such establish a prohibition, but indicates that germline intervention is highly controversial. A central point of the debate resides in the *dual-use* issue. On one side is the fear of eugenic practices, while on the other prohibiting access to therapeutic intervention collides with the right to health. The choice of the verbal form ‘could be’ indicates lack of international consensus and that determining whether germline intervention might offend human dignity is not a closed debate. As the IBC recognized recently, rapid developments in genetics require continuous reflection and re-interpretation of these principles.⁶⁴ In that sense, the *International Declaration on Human Genetic Data*⁶⁵ re-affirms a broad construction of the concept of personality. Respect for diversity, non-discrimination, non-stigmatization, and autonomy are recognized consequences of respecting human dignity.⁶⁶ Declaring the human genome to be a heritage of humanity should not entail reducing humanity to its biological dimension. The UN recognizes that ‘a person’s identity should not be reduced to genetic characteristics, since it involves complex educational, environmental and personal factors and emotional, social, spiritual, and cultural bonds with others and implies a dimension of freedom’.⁶⁷ It acknowledges the continuous evolution of the human genome and epigenetics phenomena. The human genome evolves by nature and is in constant mutation. Genetic potential is ‘expressed differently according to each individual’s natural and social environment, including the individual’s state of health, living conditions, nutrition and education’.⁶⁸

The *Universal Declaration on Bioethics and Human Rights*⁶⁹ was intended ‘to provide a universal framework of principles and procedures’ to guide states, corporations, and other public or private actors in the formulation of legislation, policies, rules, and actions in the field of bioethics.⁷⁰ It establishes the primacy of individual interests over the interests of science and society,⁷¹ consecrating a principle of maximizing benefit and minimizing harm to affected individuals.⁷² Autonomy, informed consent and

⁶¹ Universal Declaration on the Human Genome and Human Rights, adopted by the UNESCO General Conference on Nov. 11, 1997 and endorsed by the United Nations General Assembly, 53rd session, resolution A/RES/53/152, Dec. 9, 1998 [hereinafter Human Genome Declaration].

⁶² Article 1, Human Genome Declaration.

⁶³ Article 24, Human Genome Declaration.

⁶⁴ Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights, UNESCO, SHS/YES/IBC-22/15/2REV.2 (Paris, Oct. 2, 2015), at 127–8.

⁶⁵ Article 3, *International Declaration on Human Genetic Data*, adopted by the UNESCO General Conference on Oct. 16, 2003 [hereinafter Genetic Data Declaration].

⁶⁶ Article 6, Human Genome declaration; Article 7, Genetic Data Declaration; Article 11, Bioethics Declaration (see *infra* note 70).

⁶⁷ Article 3, Genetic Data Declaration.

⁶⁸ Article 3, Human Genome Declaration.

⁶⁹ Universal Declaration on Bioethics and Human Rights, adopted by the UNESCO General Conference, Oct. 19, 2005 [hereinafter Bioethics Declaration].

⁷⁰ Article 2, Bioethics Declaration.

⁷¹ Article 3, Bioethics Declaration.

⁷² Article 4, Bioethics Declaration.

privacy are also principles mentioned and developed.⁷³ Non-discrimination, justice, social responsibility, and benefit sharing are declared collective goals of humanity, to be pursued both by states and by private law actors. Protection of future generations from ‘the impact of life sciences’, including the impact on their genetic constitution, is also established as a goal,⁷⁴ as well as protection of the environment, the biosphere, and biodiversity.⁷⁵ Concerning gene editing, the primacy of individual interest is an interesting principle. It allows argument as to the inapplicability of prohibitive regulations in the interest of individual basic rights such as health, personal beliefs, and autonomy. The fact that the declaration is also intended to guide the actions of corporations and other non-state actors (public or private) is extremely important. It is a first step in establishing international patterns of conduct and responsibility independently of national implementation or in cases where jurisdiction is difficult to establish.

Recently, the IBC released an updated *Report on the Human Genome and Human Rights*,⁷⁶ recommending a moratorium on genome editing of the human germline. The report cites safety and ethical concerns as justification,⁷⁷ and issues final recommendations. First, it affirms the importance of global responsibility and governance concerning scientific and technological advances in genomics.⁷⁸ Governments and a broad range of stakeholders are invited to join forces to avoid letting the law of supply and demand determine what is or is not acceptable. It also advocates shared global standard setting and regulation,⁷⁹ and the importance of involving the scientific and bioethics community in global debate. Perhaps more controversially, the report proclaims that ‘the United Nations [...] should be responsible for making fundamental normative decisions’ and that the precautionary principle should be respected and guide decisions.⁸⁰ Finally, the report states that ‘the difference between medical and non-medical use of the new technology remains crucial’. Enhancement techniques should respect human rights and dignity, and obey the precautionary principle. Health protection and health care applications, ‘for instance through precision and personalized medicine, should be considered as content of the fundamental right of every human being to enjoy the highest attainable standard of health’.⁸¹

Historically, domestic legislators and adjudicators have transposed and interpreted UN human rights norms and principles with considerable variation. Further regional international legal sources and each country’s constitution/basic laws create an additional background to specific technological regulation.

⁷³ Articles 5 to 9, Bioethics Declaration.

⁷⁴ Article 16, Bioethics Declaration.

⁷⁵ Article 17, Bioethics Declaration.

⁷⁶ UNESCO, Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights (2015), <http://unesdoc.unesco.org/images/0023/002332/233258E.pdf> (last accessed May 17, 2017).

⁷⁷ *Id.* at 118.

⁷⁸ *Id.* at 115.

⁷⁹ *Id.* at 116.

⁸⁰ *Id.* at 117.

⁸¹ *Id.* at 122.

The Council of Europe Convention on Biomedicine⁸² addresses genetic modification in Article 13, stating that:

An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.

At first sight, this norm contains an absolute prohibition of all non-therapeutic intervention, including therapeutic intervention affecting future generations. However, the wording of the convention, in particular the expression ‘and only if the aim is not to introduce any modification in the genome of any descendants’ may support a different reading. It could also be interpreted as allowing intervention directed at medical purposes even if this may entail a modification in somatic cells passed on to descendants. This would be the case of a genetic intervention destined to correct a mutation, preventing or irradiating a severe genetically transmittable condition. The direct aim would be therapeutic, with eventual modification or improvement of future generations in that family a collateral effect. Acceptance would depend on weighting the medical benefits against the risks of the procedure, and considering the available therapeutic alternatives for the individual. The explanatory report to the Oviedo Convention,⁸³ which has interpretative value,⁸⁴ stresses that the primary goal and general interpretative guiding principle of the convention is to ‘protect the dignity and identity of all human beings’,⁸⁵ understood as protecting the biological and genetic identity of the species⁸⁶ and inspired by the principle of the primacy of the human being.⁸⁷ Arguably, this principle is honored insofar as the gene-editing objective is to prevent or correct genetic mutations which by themselves are a threat to the integrity and future of human identity.⁸⁸ The drafters of the convention did not enjoy the benefit of current scientific knowledge, which affords envisioning potential therapeutic applications. The drafters were aware of this fact, debated the possibility for creating exception, and concluded that such was premature and thus consistently stressed the need for Article 13 to be reviewed after a certain period of time to avoid precluding future gene therapy.⁸⁹ The elements of interpretation of international treaties mentioned in Articles 31 and 32 of the Vienna Convention⁹⁰ support the use of a less literal interpretative approach. Later advances in science and

⁸² Oviedo Convention, *supra* note 17.

⁸³ Council of Europe, Explanatory Report to the Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine 71–73; 89–92 (1997).

⁸⁴ *Id.*, ¶ 90.

⁸⁵ Article 1, Oviedo Convention.

⁸⁶ Article 2, Oviedo Convention.

⁸⁷ Explanatory Report, *supra* note 83, at 22.

⁸⁸ See Explanatory Report, *supra* at note 83, at 92, stating that ‘the article does not rule out interventions for a somatic purpose which might have unwanted side-effects on the germ cell line’, and thus distinguishing between aim and result of a genetic intervention.

⁸⁹ Council of Europe, Preparatory Works on the Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine 63–68 (2000).

⁹⁰ Vienna Convention on the Law of Treaties, May 23, 1969, United Nations, Treaty Series, vol. 1155, at 331.

society offer new perspectives to legal interpretation if the relevance of the literal and historic element is tempered with a dynamic legal interpretation.

The *EU Charter of Fundamental Rights* includes ‘third-generation’ fundamental rights relevant in the field of bioethics.⁹¹ The charter is addressed to the institutions and bodies of the EU and national authorities when implementing EU law. Outside these premises, protection of fundamental rights is guaranteed under national constitutional norms and traditions of member states and the international conventions they have ratified. Article 3 consecrates a personal right to respect for physical and mental integrity, including in particular in the fields of medicine and biology, ‘the prohibition of eugenic practices, in particular those aiming at the selection of persons’ and ‘the prohibition of the reproductive cloning of human beings’.⁹² Article 3 should be read in conjunction with Article 35 establishing ‘the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices’. As such, there is no direct prohibition of germline modifications. The treaty merely prohibits eugenics practices, while preventive health care is expressly included under the right to health. The distinction between eugenics and preventive medicine has to be framed under specific EU regulatory framework, and developed in national norms.

The international human rights principles and norms here explored address issues such as protection of human genetic identity, biodiversity, and environmental protection. Genetic intervention raises moral objections on several grounds. One of the major arguments points to the moral inadmissibility and biological dangers of attempts to modify human nature. Defense of the biological integrity of the species or the common genetic heritage of humanity has been transposed from the field of theology and philosophy and entered the international human rights arena. The departure point has been a static vision of human biology and distinctions between ‘natural’ and ‘technological’. Counterintuitively, this distinction is difficult to establish in precise scientific terms. As recently mentioned in a National Academies Report, ‘the human genome is not entirely ‘human’, as it includes Neanderthal and Denisovan DNA. [...] Nor does it exist in any single, static state. [...] There is no single human genome shared by all of humanity’.⁹³ Furthermore, since germline modifications are only transmitted to descendants, detrimental population scale effects are unlikely and would take many generations.

Concerning gene editing of animals and plants, either for laboratory use, industrial production purposes, or release in the environment, the technology may raise ethical issues concerning the ethical treatment of animals; conflict with the values of preservation of biodiversity and ‘natural’ ecosystems; and raise human rights concerns connected with the right to health. This is due to perceptions of potential for health risks associated with introduction of edited organisms in the food chain and development of dangerous streams of bacteria and viruses.

This fundamental rights framework forms the background to regulation of science. In the next section, we consider the existing rules regulating scientific activities in the

⁹¹ Charter of Fundamental Rights of the European Union (2000/C 364/01), OJ C 364/1 [hereinafter EU Charter].

⁹² Article 3 (2), EU Charter.

⁹³ National Academies, *supra* note 19, at 94–5.

USA, the EU, and the UK, questioning whether these need to be adapted in order to address gene-editing-specific characteristics and possibilities.

IV.B. Applying Existing Regulations to Gene Editing

The rapid progress in gene-editing technology has left legislators and regulators around the world trying to find out how, or if at all, to regulate these advances and their resulting applications. As with many other fields of technology, the applications of gene editing in plants and medicine are in the spotlight of the enfolding debates. The debates concerning gene editing have landed on top of unsettled debates in Europe. Areas of technology regulation where interpretation of rules is subject to heated legal and societal arguments. In this section, we have selected two important areas of regulatory action to focus our analysis. First, we will address the question of the legal characterization of gene edited plants and the possible applicability of rules concerning genetic modified organisms. Second, we will briefly consider the use of gene-editing technology in a medical and veterinary setting.

IV.B.a. Gene-Edited Plants GMO 2.0 or Something Else?

Much of the criticism of GMOs, and much of the regulation developed 20–30 years ago, focused on transgenics in which genetic material from unrelated species is added to create new traits in a plant or animal. However, newer breeding techniques (NBT) offer scientists an easier way to do cisgenic breeding. Put simply, these techniques involve no ‘foreign’ DNA and thus allow the development of new plant and animal varieties.⁹⁴ The resulting challenge to current legislation can be described as follows: NBTs such as CRISPR/Cas9, TALENs, and ZFN do not fit neatly into the GMO definitions crafted by the various regulatory agencies around the world. Its proponents say gene editing is similar to mutagenesis, which is not regulated (hundreds of mutagenized crops are sold as organic), but faster and more precise. The regulatory process remains fluid.

The need for new regulation covering gene-editing technology in the plant sciences is particularly debated and evident in the European Union. Administrative authorities in some EU countries do not consider gene-edited plants to fall under the GMO definition. For example, the Swedish Board of Agriculture (*Jordbruksverket*), upon request from research groups and in two separate decisions, has stated that in their interpretation the GMO legal definition does not encompass plants in which the genome has been edited using the CRISPR-Cas9 technology.⁹⁵ In France, in a case opposing farmers’ organizations and environmentalist NGO’s to the French Government, a referral on the matter is currently pending before the CJEU.⁹⁶ The referral is expected to clarify the concept of GMO contained in Directives 2001/18/EC⁹⁷ and 2002/53/EC,

⁹⁴ See *How are Governments Regulating CRISPR and New Breeding Technologies (NBTs)?* GENETIC LITERACY PROJECT, <https://gmo.geneticliteracyproject.org/FAQ/how-are-governments-regulating-crispr-and-new-breeding-technologies-nbts/> (last accessed Jan. 10, 2017).

⁹⁵ Decisions available (in Swedish) http://www.umu.se/digitalAssets/171/171718_beslut-umea.pdf, and http://www.umu.se/digitalAssets/171/171719_beslut-upsala.pdf (last accessed May 23, 2017).

⁹⁶ Request for a preliminary ruling (France) lodged, Oct. 17, 2016 (CJEU Case C528/16).

⁹⁷ Directive 2001/18/EC of the European Parliament and of the Council of Mar. 12, 2001 on the deliberate release into the environment of genetically modified organisms (OJ 2001 L 106, at 1).

and whether uses of gene editing technology can be subsumed to such legal definition.⁹⁸

The matter is also debated in other jurisdictions. In April 2016, the US Department of Agriculture (USDA) decided that it would not regulate a mushroom and a new type of corn genetically modified with the gene-editing tool CRISPR/Cas9, making them the first CRISPR-edited crops to be approved by the US government. According to the agency's Animal and Plant Health Inspection Service, these crops—and about 30 other plants they have reviewed—do not qualify as something the agency must regulate (once a crop passes USDA reviews, it may still undergo voluntary review by the US Food and Drug Administration).⁹⁹ Biotechnology critics in the USA have therefore called NBTs 'hidden GMOs' and examples of 'extreme engineering', and are pushing to regulate them under a general GMO umbrella, while biotechnology supporters assert that regulating them as GMOs would inhibit innovation.¹⁰⁰

Hence, it can be said that both current EU Directives and corresponding US laws do not sufficiently embrace the new interface between genetic engineering and conventional breeding. Although Directive 2001/18/EC encompasses both process- and product-related stipulations, it is commonly interpreted as a strictly process-based piece of legislation.¹⁰¹ Since these new techniques are closer to conventional breeding than common genetic engineering, many European commentators argue, like their US colleagues, that relevant regulations should be phrased and interpreted with more focus on the resulting product, rather than the process, and that legal guidance on how to apply 'the decade-old legislation is urgently needed'.¹⁰²

Since scientists and companies typically operate internationally and the development of regulation on gene editing and NBT is facing several hurdles and inconsistencies on a global level, one study has compared current EU legislation with existing frameworks in other countries and discussed ideas for an alternative regulatory system.¹⁰³ The most recent version of that study, published in June 2015, found that the next few years will be defining for the regulatory status of NBTs in countries outside the EU. In that regard, the study emphasized that 'several countries are in varying stages of reviewing the science behind NBTs and their regulatory status, it is clear that most countries are waiting for other countries or international organizations to take a position; the EU plays an important role in this waiting game'. The reluctance of several countries to discuss these topics is linked to political and economic issues. Since NBTs are virtually untraceable, allowing their use may result in overall de facto exportation bans to countries with more restrictive regulations. Therefore, the matter should be debated on a global level by initiatives governing international trade, such as

⁹⁸ Council Directive 2002/53/EC of June 13, 2002 on the common catalog of varieties of agricultural plant species (OJ 2002 L 193, at 1).

⁹⁹ *Id.*

¹⁰⁰ *Id.* See also Heidi Ledford, *Gene-Editing Surges as US Rethinks Regulations*, 532 NATURE 158–9 (2016).

¹⁰¹ Thorben Sprink et al., *Regulatory Hurdles for Genome Editing: Process- vs. Product-Based Approaches in Different Regulatory Contexts*, 35 PLANT CELL REP. 1493–506 (2016).

¹⁰² *Id.*

¹⁰³ Schuttelaar & Partners, *The Regulatory Status of New Breeding Techniques in Countries Outside the European Union* (2015), <http://www.nbtplatform.org/background-documents/rep-regulatory-status-of-nbts-ou-side-the-eu-june-2015.pdf> (last accessed Jan. 10, 2017).

the World Trade Organization.¹⁰⁴ Finally, it is noteworthy that NBTs also challenge the interplay between the systems for plant variety protection and patents (see below in Section IV.D.d).

IV.B.b. Medical and Veterinary Applications

In the area of medical applications in humans, gene-editing technology also poses an enormous challenge to existing regulations throughout the world. Gene editing offers unprecedented opportunities for preventive medicine, affording the possibility to correct genetic mutations and eradicate congenital disease.¹⁰⁵ Eventually gene-editing technology will reach a safe level that permits clinical applications. In that event countries considering allowing such preventive medicine intervention would have to consider the need to form a global consensus ‘because thinking about germline gene modification involves ethical, social, and evolutionary considerations for all of humankind’.¹⁰⁶

For example, the recent announcement of gene editing in unviable embryos¹⁰⁷ has prompted a torrent of criticism, fueled fears of eugenic futures, and re-ignited the human enhancement debate. As mentioned before, two distinct groups of high-profile scientists have called for a moratorium on editing germline genomes, arguing that research which produces heritable edits to the human genome must not proceed until the risks are better understood.¹⁰⁸ Similarly, the *European Group on Ethics in Science and New Technologies* (EGE) issued a *Statement on Gene Editing* emphasizing that for ‘some members of the EGE, human germline gene modification for reproductive purposes cannot be ethically justified’, and that they therefore ‘call for upholding the prohibition that reflects, among others, Article 3 of the *EU Charter*; because of the blurring lines between basic and applied research, some also call for a moratorium on any basic research involving human germline gene modification until the regulatory framework is adjusted to the new possibilities’.¹⁰⁹ However, the statement then also points out that for ‘other members of the EGE, there may be positions worth considering which would justify continued research’. Due to the diversity of views, they then call for a broad public debate and urge the EU Commission to request a EGE opinion on ‘the inextricably linked ethical, scientific and regulatory issues pertaining to germline and somatic cell gene modification’.¹¹⁰

This view is also shared by a recent study, which further notes—as with NBTs—an enormous worldwide diversity of attitudes and very different legislation on genetic technology in humans, such as germline genetic modification, preimplantation genetic diagnosis, somatic gene therapy, embryonic stem cell research, research cloning, and reproductive cloning.¹¹¹ The authors emphasize that public acceptance may change

¹⁰⁴ *Id.* at 46.

¹⁰⁵ Motoko Araki & Tetsuya Ishii, *International Regulatory Landscape and Integration of Corrective Genome Editing Into In Vitro Fertilization*, 12 *REPROD. BIOL. & ENDOCRINOL.* 108 (2014).

¹⁰⁶ *Id.* at 10.

¹⁰⁷ Liang et al., *supra* note 1.

¹⁰⁸ Lanphier et al., *supra* note 16; Baltimore et al., *supra* note 16.

¹⁰⁹ European Group on Ethics in Science and New Technologies, *Statement on Gene Editing*, https://ec.europa.eu/research/ege/pdf/gene_editing_ege_statement.pdf (last accessed Feb. 6, 2017).

¹¹⁰ *Id.*

¹¹¹ R. Isasi, E. Kleiderman & B. M. Knoppers, *Editing Policy to Fit the Genome?*, 351 *SCIENCE* 337–39 (2016).

as the benefits of genome editing emerge for disease prevention and that the collective sum of individual decisions could constitute a de facto policy.¹¹² However, the authors admonish that ‘the task of adopting policy guidance for the acceptability (if at all) of germline interventions is more than just editing policy to fit individual genomes or circumstances’.¹¹³

Conversely, in the USA the above mentioned recent *National Academies Report* recommends that clinical trials using heritable germline genome editing should be permitted, and that regulatory approval requirements should encompass absence of reasonable alternative; prevention of a serious disease or condition; and credible data on safety and efficiency.¹¹⁴

Clearly, to address these concerns requires a thorough review of regulatory frameworks. In this context, attention should be given to the changing patterns of use of technology, since ‘applying normative systems only to traditional hierarchical social structures will increasingly overlook significant numbers of relevant actors and that new ways of engaging users of technology in moral communities may need to be found’.¹¹⁵

In addition to covering gene-editing science as such, regulation will also have to include changes to regulatory frameworks for approval of medicines and therapies, such as USA/FDA regulations and EU/EMA regulations. In the USA, the FDA is already in the process of enacting new regulations,¹¹⁶ and presumably the EU/EMA is also reconsidering the Regulation on Advanced Therapies¹¹⁷ and other applicable EU legislation.¹¹⁸ Presently, the EMA has launched an ongoing revision process seeking to adapt its overarching guideline on medicinal products containing genetically modified cells to the advances in gene-editing technology.

A new regulation on clinical trials has been enacted,¹¹⁹ interestingly maintaining without further clarification a broad prohibition for gene therapy clinical trials ‘which result in modifications to the subject’s germ line genetic identity’,¹²⁰ in force under the

¹¹² *Id.* at 339.

¹¹³ *Id.*

¹¹⁴ National Academies, *supra* note 19, at 145.

¹¹⁵ Nuffield Council on Bioethics, *Genome Editing: An Ethical Review* (2016), <http://nuffieldbioethics.org/project/genomeediting/ethical-review-published-september-2016> (last accessed Mar. 10, 2017) at 119.

¹¹⁶ Sarah Zhang, *The FDA Wants to Regulate Gene-Editing That Makes Cows Less Horny*, THE ATLANTIC, 2017, <https://www.theatlantic.com/science/archive/2017/01/the-fda-wants-to-regulate-gene-edited-animals-as-drugs/513686/> (last accessed Feb. 6, 2017).

¹¹⁷ Regulation (EC) No 1394/2007 of the European Parliament and of the Council of Nov. 13, 2007 on Advanced Therapy Medicinal Products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 324/121, <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF> (last accessed May 4, 2017).

¹¹⁸ European Commission, *EudraLex - Volume 1 - Pharmaceutical Legislation for Medicinal Products for Human Use*, <http://ec.europa.eu/health/documents/eudralex/vol-1.en> (last accessed May 4, 2017); European Commission, *EudraLex - Volume 5 - Pharmaceutical Legislation for Medicinal Products for Veterinary Use*, <http://ec.europa.eu/health/documents/eudralex/vol-5.en> (last accessed May 4, 2017).

¹¹⁹ Regulation (EU) No 536/2014 of the European Parliament and of the Council of Apr. 16, 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. [Regulation on Clinical Trials].

¹²⁰ Article 90, Regulation on Clinical Trials. See also recital 75, Regulation on Clinical Trials.

previous legislation.¹²¹ Rules concerning compassionate use (Article 83 of regulation 726/2004/EC) and named patient-basis treatment programs under national law are also part of this complex regulatory framework and depending on how these will be applied may offer routes to discrete and progressive use of gene editing in a therapeutic setting. Other regulations to consider and interpret in light of gene editing include the tissues and cells directive,¹²² applicable to the donation, procurement, and testing of biological samples used as starting materials for genetic interventions.

IV.B.c. The UK Approach

In Europe, the UK regulatory approach has unique features worthy of mention. The UK has neither ratified nor signed the Oviedo Convention. It has also recently initiated procedures to leave the EU. However, it is a member of the EPO and likely to join the Unified Patent Court (UPC).¹²³ The UK was also the first country in the world to authorize mitochondrial replacement, a technique entailing genetic modifications transmittable to future generations.

The *Human Fertilisation and Embryology Act* was recently amended to introduce the possibility for implantation of embryos obtained through the process of mitochondrial donation. As noted above, the UK became the first country to directly permit implantation of such embryos. The procedure is allowed as a way to avoid severe genetic conditions.¹²⁴ By replacing the unhealthy mitochondria of the mother with healthy mitochondria from a donor, a healthy child can be born with 99.9 per cent of the DNA of its parents, and 0.1 per cent of the DNA of the donor. The first license to perform the procedure in the UK has been granted.¹²⁵ Previously, the technique had been performed by John Zhang and his team from the *New Hope Fertility Center* (New York, USA). US law does not allow mitochondrial transplants. The procedure was performed in Mexico, where it is not directly regulated. A male child was born on April 6, 2016, showing no signs of Leigh syndrome, the mitochondrial transmitted disease carried by the mother.¹²⁶

During parliamentary debates, use of words such as *genetic modification*, *editing*, or *manipulation* was carefully avoided. Debate focused mostly on potential benefits in saving lives and avoiding the pain and suffering associated with severe diseases. However, the technology does entail modification of the human genome transmittable to future

¹²¹ Article 9 (6), Directive 2001/20/EC of the European Parliament and of the Council of Apr. 4, 2001 on the approximation of the laws, regulations, and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 1.5.2001, at 34.

¹²² Directive 2004/23/EC of the European Parliament and of the Council of Mar. 31, 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells (OJ L 102, 7.4.2004, at 48–58).

¹²³ Unified Patent Court, *Update on UPC ratifications – UK signals green light* (2016), <https://www.unified-patent-court.org/news/update-upc-ratifications-uk-signals-green-light> (last accessed May 4, 2017).

¹²⁴ Human Fertilisation and Embryology Act 2008 c 22, Section 35A ‘Mitochondrial donation’.

¹²⁵ Human Fertilization and Embryology Authority, *Licence Committee—Minutes* (2017), <http://ifqtesting.blob.core.windows.net/umbraco-website/1331/2017-03-09-licence-committee-minutes-variation-of-licensed-activities-to-include-mitochondria-pronuclear-transfer-pnt-centre-0017.pdf> (last accessed May 4, 2017).

¹²⁶ John Zhang et al., *First Live Birth Using Human Oocytes Reconstituted by Spindle Nuclear Transfer for Mitochondrial DNA Mutation Causing Leigh Syndrome*, 106 FERTIL. & STERIL. e375–76 (2016).

generations. Arguments used to allow the procedure can equally apply to therapeutic uses of gene editing. The issue of whether gene editing should be accepted on a similar basis has already been raised,¹²⁷ and the UK *Human Fertilisation and Embryology Authority* has authorized gene-editing research on human embryos.¹²⁸

IV.C. Patent Issues and their Regulatory Role

Patent rights are an administrative concession granting the right to prevent third parties from making, using, offering for sale, selling, or importing for these purposes a patented product or a product obtained by the patent process. Grant of a patent also entails the right to assign the patent, or transfer by succession, and to conclude licensing agreements. A patent does not establish the right to use technology or to place on the market products embedding the patent. It does not imply an official *stamp of moral approval* on technology and its various possible uses. However, patent eligibility rules indirectly exercise a regulatory function. Patent rights are instrumental to the development of a given technology. Although alternative incentive mechanisms exist and innovation may occur regardless of patent rights, large investments in technological development are usually dependent on the existence of exclusionary rights. Technology is developing at a fast pace and industrial actors are keen on developing mechanisms to avoid an eventual impasse created by intertwined rights and long litigation. Under this setting, it will be of importance whether patents covering CRISPR/Cas9 and other gene-editing technology remain in force and which actors own or obtain licenses to exclusionary rights.

IV.C.a. Patents and the Ghost of Eugenic Futures

Slippery slope arguments and debates on human nature are a constant in debates concerning scientific and technology advances in human genetics. In previous parts of this paper, we analysed general ethical perspectives (Section II) and the human rights framework constructed to protect the human genome and its legal conceptualization as heritage of humanity and its preservation as a legal value with fundamental right dignity. In this section, we analyse similar issues and debates from a perspective of interpretation and application of patent law rules on patentable inventions.

Patent law being a very dynamic field of law is likely to be one of the first legal areas where ethical compliance of gene editing with the fundamental legal principles and regulatory norms will be confronted. Patent law is so far the most universal legal incentive to innovation, and in this sense it assumes an indirect policy function, visible in the inclusion of extra-economic considerations in patentability rules. These considerations are intended to ensure compliance with ethical values and scientific needs by imposing restrictions on the patentability of certain inventions, transposing the ethical debate to patent law. This section explores how European patent eligibility norms might apply to gene editing.

¹²⁷ Progress Educational Trust, *From Three-Person IVF to Genome Editing: The Science and Ethics of Engineering the Embryo*, <http://www.progress.org.uk/conference2015> (last accessed May 4, 2017).

¹²⁸ Authorization was granted to Kathy Niakan, stem cell researcher at the *Francis Crick Institute*. The goal is to determine which genes are crucial for healthy cell division, and then use that knowledge to screen embryos, potentially preventing miscarriages and aiding fertility. The embryos concerned cannot be older than seven days and will not be implanted. See The Francis Crick Institute, *HFEA Approval for New 'Gene Editing' Techniques*, (2016), <https://www.crick.ac.uk/news/science-news/2016/02/01/hfea-decision/> (last accessed Mar. 4, 2017).

Modifying the germline genetic identity of human beings is expressly excluded from patentability in Europe.¹²⁹ This entails that method claims directed at such developments of gene-editing technology may not be eligible for patent protection. Somatic cell gene methods in principle will not face such objections. These concern modifications in somatic cells by means of recombinant DNA and only operate in the cells of the recipient but will not be carried on to descendants. Nevertheless, it will still be necessary to evaluate such intervention in light of the general broader ‘ordre public’ and morality patentability exception, since such intervention can also raise ethical concerns. As a point of legal interpretation, it can be argued that all intervention involving the human body carries risks and potential (known and unknown) side effects. Objections based on safety and danger for humanity of unintended side effects or mutations changing the *common human genetic heritage* are merely a question of weighting therapeutic benefit against risk, something present in every medical decision (e.g. use of antibiotics or vaccination). The risks are unknown, but even germline editing will only be carried on to descendants, making wider population effects a distant scenario. Technology will continue to develop and might afford the possibility to correct/reverse unwanted off-target modifications. Insofar as therapeutic applications for severe health conditions are concerned, no substantial difference exists between the well-established practice of parental consent to perform conventional therapy or surgery to treat or manage a disease and the use of gene-editing technology to prevent future generations from ever developing the disease. In such situations, it can be argued that the (future) individual has the right to health and access to treatment and hence legal guardians have at least the right (if not the duty) to procure the best medical treatment available. Parental refusal of treatment is subject to specific regulations and mostly only acceptable under exceptional circumstances—eg conflict with other fundamental rights—and thus the same reasoning might be extended by analogy to the use of safe and non-experimental preventive gene therapy.

Gene editing might also be used outside purely therapeutic situations. The issue of acceptability of human enhancement has for a considerable time been the object of legal philosophical debates. Rawls argued that ‘the parties want to ensure their descendants the best genetic endowment’¹³⁰ arguing that by virtue of the difference principle¹³¹ ‘greater abilities are a social asset to be used for the common advantage’,¹³² and concludes that ‘society is to take steps at least to preserve the general level of natural abilities and to prevent the diffusion of serious defects’.¹³³ This line of reasoning would endorse all genetic intervention (including gene editing) as long as such intervention has the purpose of avoiding serious disease or disability. Naturally, this reasoning implies a pre-determination of the legal concepts of disease, disability, and therapy. Dworkin goes further; contending that morality requires society to allow parents to genetically enhance their children so that they may have broader choices and greater chances of

¹²⁹ Rule 28(b) EPC implementing Regulations; § 6 (2) (b) Biotechnology Directive.

¹³⁰ JOHN RAWLS, *A THEORY OF JUSTICE* 92 (1999).

¹³¹ See RAWLS, *supra* note 130, at 65 and JOHN RAWLS & ERIN KELLY, *JUSTICE AS FAIRNESS* 76 (2001).

¹³² RAWLS, *supra* note 130, at 92.

¹³³ See also ALLEN BUCHANAN, *FROM CHANCE TO CHOICE* 302 (2000), defending the case that genetic enhancements are morally permissible and laudable, and that therapeutic genetic intervention to prevent disabilities is a moral imperative.

succeeding in life.¹³⁴ On the other hand, Fukuyama warns that genetic enhancement is a threat to liberal democracy due to the possibility that it will alter human nature, arguing that genetic engineering should be subject to strict regulatory constraints and its admissibility limited to clearly therapeutic treatments.¹³⁵ Habermas wrote that such intervention denies the child the possibility to be revised in adult life by ‘critical reappraisal’, denying a person’s ability to be ‘the undivided author of his own life’.¹³⁶ More recently, enhancement proponents and transhumanism adepts counterargue that these objections would equally apply to many parenting practices not generally considered controversial.¹³⁷ Some authors defend the right to enhancement and a moral imperative to eradicate disease.¹³⁸

Modifying the germline genetic identity of human beings is expressly mentioned as an exclusion from patentability.¹³⁹ Recitals 38 and 40 of the Biotechnology Directive express legislative intent ‘to exclude unequivocally from patentability processes for modifying the germ line genetic identity of human beings’.¹⁴⁰ Patent norms do not make functional distinctions, meaning that the purpose of an intervention—the actual use claim in the patent application—is immaterial. Under this literal interpretation, all interventions in germ cells will encounter patentability hurdles, including in the abstract, even those with purely therapeutic purposes. Somatic cell intervention would fall outside the scope of the specific provision; however, these still require an assessment of their moral conformity under the general ‘ordre public’ and morality clause.¹⁴¹ As follows from the European legal tradition, further interpretative elements can, and should when appropriate, be taken into consideration by adjudicators. Below we consider systemic elements such as the human rights framework and issues of legal coherence.

IV.C.a.i. Patentability and Human Dignity. Interpretation of the Biotechnology Directive cannot be blind to the EU Charter and the international human rights treaties signed by some or all member states. Moreover, these are also relevant to the EPO’s interpretative praxis. However, because the grant of a patent is independent from administrative authorizations to market products or conduct medical procedures, patentability cannot be denied simply based on legal prohibition.¹⁴² This entails that a specific ethical debate has to be developed within the European patent system for purposes of applicability of patent eligibility norms.

As mentioned above, a considerable body of international norms has been enacted with the purpose of protecting ‘human nature’.¹⁴³ These are problematic because the concept of *human nature* is culturally biased and historically relative. It can be understood in a strict biological sense, but also culturally and socially. Evolution and

¹³⁴ RONALD DWORKIN, SOVEREIGN VIRTUES: A THEORY AND PRACTICE OF EQUALITY 448–49 (2000).

¹³⁵ FRANCIS FUKUYAMA, OUR POSTHUMAN FUTURE 210 (2002).

¹³⁶ JÜRGEN HABERMAS, THE FUTURE OF HUMAN NATURE 63 (2003).

¹³⁷ Nick Bostrom & Rebecca Roache, *Ethical Issues in Human Enhancement* in NEW WAVES IN APPLIED ETHICS 120–52 (Jesper Ryberg, Thomas S. Petersen & Clark Wolf eds., 2008).

¹³⁸ Julian Savulescu et al., *The Moral Imperative to Continue Gene Editing Research on Human Embryos*, 6 PROTEIN & CELL 476–79 (2015).

¹³⁹ Rule 28(b) EPC implementing Regulations; Article 6 (2) (b) Biotechnology Directive.

¹⁴⁰ Recital 40 Biotechnology Directive.

¹⁴¹ Article 6 Biotechnology Directive and Article 53 (a) EPC.

¹⁴² Article 53 (a) EPC, Article 6 (1) and recital 14 Biotechnology Directive.

¹⁴³ See above section 3.1.1

epigenetics show that human nature is not a static biological reality, but rather it evolves and is deeply influenced by environmental factors. For legal interpretation purposes, it is not possible to rely on a biological notion of a human being to distinguish *natural* from *technological*. The assertion that germline intervention is an offense to human dignity is highly debatable when the aim is to protect future generations from severe incurable diseases. The right to the highest attainable standard of health extends to preventive medicine, while the right to education, and fruition of the results of science and technology, would further protect those wishing to change their physical, emotional, and social *human nature*.

Another aspect to consider is that pursuant to the limitation imposed in Article 6 of the Biotechnology Directive, any gene-editing activity that results in the destruction of an embryo is not patentable. According to the CJEU, this limitation would even apply if destruction occurred at an undetermined historical moment and does not form part of the claimed invention, such as described in the claims.¹⁴⁴ However, Recital 42 of the Biotechnology Directive states that ‘such exclusion does not affect inventions for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it’. The CJEU, in *Brüstle*¹⁴⁵ and *ISCC*,¹⁴⁶ has provided a broad interpretation of the legal concept of *embryo*.¹⁴⁷ Intervention at the blastocyst stage is intervention in an embryo. Any intervention could be considered medically useful to an embryo if it cures, eliminates, prevents, or ameliorates a disease, impairment, or diminished capacity (including pain, discomfort, and other symptoms). This entails that any intervention with a minimum medical content or objective cannot be excluded from patentability for being offensive to human dignity.

Concerning the patentability of enhancement processes, under a strict literal interpretation germline alteration is absolutely excluded, and genetic somatic intervention is barred because it does not have a therapeutic purpose. However, arguably an intervention may be useful to an embryo if it provides results that increase well-being and life quality, even if these are generally understood as being beyond health. The language chosen does not point to the concept of health but rather to the concept of usefulness. A utilitarian vision of genetic intervention does point in a much broader direction than linkage to strictly health-related issues. Delimitation of the legal concept of enhancement in the sense of induced human evolution, as proposed, would be useful.¹⁴⁸

As mentioned above, the EPO has accepted patents on gene editing. However, these are still broad claims. Concerning specific uses, some jurisdictions will likely be more inclined to accept patentability than others, eventually leading to divergent interpretations and a referral to the CJEU.

IV.C.b. Medical Methods: Personalized Medicine or Enhancement?

Previously, we considered whether gene-editing patent claims can be excluded on morality and ‘ordre public’ grounds. Here we will address whether methods for gene

¹⁴⁴ Nordberg & Minssen, *supra* note 18.

¹⁴⁵ Case C-34/10, *Oliver Brüstle v Greenpeace e.V.*, EU:C:2011:669.

¹⁴⁶ Case C-364/13, *International Stem Cell Corporation v Comptroller General of Patents*, EU:C:2014:2451.

¹⁴⁷ Nordberg & Minssen, *supra* note 18.

¹⁴⁸ Ana Nordberg, *Defining Human Enhancement: Towards a Foundational Conceptual Tool for Enhancement Law*, 25 J. L. INFO. & SCI. (2017).

editing with health-related purposes can be patentable. Article 53 (c) EPC precludes patentability of methods for treatment and diagnostic methods. The rule only concerns method claims: apparatus claims are not excluded,¹⁴⁹ and product claims directed to substances or compositions for use in methods are expressly accepted. These remain patentable as long as the patentability requirements of novelty, inventive step, and industrial application are fulfilled.¹⁵⁰ Patents may be granted for surgical, therapeutic, or diagnostic instruments or any apparatus for use in such methods.¹⁵¹ Moreover, the *medical methods exception* only prevents patentability of methods for (i) treatment of the human or animal body by surgery, (ii) treatment of the human or animal body by therapy, and (iii) diagnostic methods practiced on the human or animal body. Therapeutic methods to be applied either to plants, deceased bodies, or prosthetics not permanently attached to a body do not fall under this provision.¹⁵²

A key element of this provision is whether the excluded methods are performed in contact with the human body. In principle, gene-editing method claims will not be refused as long as these are not performed in contact with the body. However, the mere presence of a patient is enough to satisfy the criteria. A further cumulative requirement for the exception to operate is that the method is either a method for diagnosis or treatment or a method for surgery.

The concept of therapy is construed broadly. Methods are therapeutic if these cure a disease or a malfunction of the human body, or have a prophylactic purpose.¹⁵³ This means any intervention is designed to cure, alleviate, remove, or lessen the symptoms of, and prevent or reduce the possibility of, contracting any disorder or malfunction,¹⁵⁴ even if the symptoms are caused by natural circumstances, or are a response to environmental conditions.¹⁵⁵ A functional link or physical causality must exist between intervention and a therapeutic effect produced on the body.¹⁵⁶

Methods with dual use will be patentable, but only if claims are restricted to non-therapeutic use and a clear distinction can be established between therapeutic and non-therapeutic effects.¹⁵⁷

Use of gene-editing technology to improve health and well-being is less controversial than other uses of the technology. The rights to life and access to health care override some objections. However, as far as method claims are concerned, patentability will be limited to non-therapeutic applications. Furthermore, all methods of surgery are

¹⁴⁹ T-712/93 *Joint Medical Products/Ball and Socket Bearing for Artificial Joint* [14.04.1997] unpublished.

¹⁵⁰ Article 53 (c) EPC, last sentence.

¹⁵¹ See for all EPO Guidelines for examination, part C, ch. IV, 4.8.

¹⁵² T-24/91 *Thompson/Cornea* [05.05.1994] OJ EPO 1995, 512.

¹⁵³ G1/04 *Diagnostic Methods* [2006] OJ EPO 334; T19/86 *Duphar/Pigs II* [1989] OJ EPO 25; T290/86 *ICI/Cleaning Plaque* [1992] OJ EPO 414; T438/91 *Meiji/Feeds* [17.10.1994] unpublished.

¹⁵⁴ T24/91 *Thompson/Cornea* [1995] OJ EPO 512.

¹⁵⁵ T81/84 *Rorer/Dysmenorrhea* [1988] OJ EPO 207, reasons 3; Cf. T385/09 *Lely/Method of Cooling Animals* [25.11.2010] unpublished, reasons 3.6.

¹⁵⁶ T329/94 *Baxter/Blood Extraction Method* [1998] OJ EPO 241. See below the EPO board's jurisprudence concerning implants and prosthetic devices.

¹⁵⁷ T144/83 *Du Pont/Appétit Suppressant* (n 4); T36/83 *Roussel-Uclaf/Thenoyl Peroxide* (n 4); T469/94 *MIT/Perception of fatigue* (n 13). Cf. T116/85 *Wellcome/Pigs I* (n 30); T780/89 *Bayer/Immunostimulant* [1993] OJ EPO 440; T-438/91 *Meiji/Feeds* (n 9); T-290/86 *ICI/Cleaning Plaque* (n 4); T1077/93 *L'Oreal/Protection Against UV Radiation* (n 4); T-1635/09 *Bayer/Composition for Contraception* [2011] OJ EPO 542.

excluded, regardless of their objective. This is because the determinant factor in characterization as surgery is the health risk involved in a procedure (a substantial, non-routine intervention on the human body requiring medical expertise) and not other factors such as the purpose of the procedure or intensity of tissue perforation.¹⁵⁸

Human rights-based legal thinking tends to frame the issue of gene editing in two separate veins of reasoning: biosafety and prohibition of eugenics. In the abstract, it is simple to weave out what is safe and presents a medical benefit from past horrific experiments and eugenic doctrines. In reality, attempts to regulate gene editing face the dual-use problem. Moreover, it is not straightforward to distinguish personalized preventive medicine from human enhancement. In practice, concrete determination depends on non-technical elements, such as social constructions of normality and human nature.¹⁵⁹ As a result, emerging technology will pose considerable interpretative difficulties to application of the medical methods patent exclusion.

IV.C.c. Patentability of Edited Plants

As indicated before, an increasingly important area of application for gene-editing technology is the agricultural sciences and plant sciences. Innovative plant breeding is not only important for producing more and better food for a rapidly increasing global population by the construction of transgenic crop varieties engineered for resistance to specific diseases, but also for enhanced nutritional properties and other desirable traits. Indeed, building upon rapid advances in synthetic biology and gene editing, modern plant science is also becoming increasingly important in many other areas of industrial applications, such as drug development, energy production, and space science.¹⁶⁰ Such inventions can be protected both by patents and by plant variety rights (PVR).¹⁶¹

Article 27(3)(b) of the TRIPS Agreement obliges countries to provide minimum protection for plant varieties 'either by patents or by an effective sui generis system or by any combination thereof'. Moreover, WTO members have the choice to exclude 'essentially biological processes for the production of plants' from patentability.¹⁶² Hence, some South American and European countries along with China and India take a highly restrictive approach, excluding certain plant-related inventions from patentability.¹⁶³ In contrast, the US Patent Act is (still) far more permissive and includes no explicit statutory exemption of plant-related inventions. Not only can claims directed to plants *as such* be protected but also plant parts, such as seeds and seedlings, and methods for the production of plants, provided that all patentability requirements are met. The US Supreme Court explicitly confirmed in *J.E.M. Ag Supply v Pioneer Hi-Bred*¹⁶⁴ the long-standing practice of the USPTO of granting utility patents on plants.¹⁶⁵

¹⁵⁸ G1/07 Enlarged Board of Appeal (EBA) in *Medi-Physics/Treatment by Surgery*, order 1.

¹⁵⁹ Generally see ANA NORDBERG, PATENTING NANOMEDICINE IN EUROPE: APPLYING THE 'MEDICAL METHODS EXCEPTION' TO EMERGING TECHNOLOGIES (2017).

¹⁶⁰ Minssen & Nordberg, *supra* note 18.

¹⁶¹ Sometime also referred to as breeders' rights.

¹⁶² Cf. Standing Committee on the Law of Patents, 13th Session Geneva, Mar. 23 to 27, 2009 'Exclusions from Patentable Subject Matter and Exceptions and Limitations to the Rights', at □ 59.

¹⁶³ Minssen & Nordberg, *supra* note 18, at 81–98.

¹⁶⁴ *J. E. M. Ag Supply, Inc. v. Pioneer Hi-Bred International, Inc.*, 534 U.S. 124 (2001).

¹⁶⁵ Franz-Josef Zimmer & Markus Grammel, *Plant Patents in Europe*, 34 BIOTECHNOL. L. REP. 121–31 (2015).

Whereas national laws governing the *patentability* of plants may vary significantly among countries, the need to protect the IP rights of plant breeders was acknowledged by legislators as early as the 19th century.¹⁶⁶ Today, PVR and patents form a synergistic and complementary IP system.¹⁶⁷ PVR protects new plants as a whole but cannot protect single parts (eg a specific gene), while patents protect parts, but (in general) not whole plants.¹⁶⁸ The original intention was for patents and PVR to protect different subject matter in ways appropriately adapted to the needs of different industries. Until a few decades ago, plant breeding was conducted by traditional cross-breeding methods based on empirical *trial and error* experimentation, and plant-related innovations were almost exclusively protected by PVR. The problem is, however, that the plant industry has rapidly turned toward incorporating synthetic and molecular breeding and technically advanced selection systems.¹⁶⁹ Today's plant innovations are developed using sophisticated science technology, including advanced gene-editing technology, cell biology, genome and proteome research, gene mapping, marker-assisted breeding, and hybridization. The development of beneficial traits may thus be expensive, time consuming, and risky.¹⁷⁰

However, it is quite usual for breeders to enhance their own breeding lines by resorting to beneficial traits from their competitors' varieties, including commercially available protected plant varieties where previous gene editing cannot be traced back. This stands in conflict with the interests of patent holders in the biotechnology industry, and their own costly, risky, and time-consuming R&D efforts.¹⁷¹ As a consequence, the distinction between PVR protection and patent protection has become blurred, with some commentators warning that this 'disrupts the equilibrium in the reward systems of classical plant breeders and the biotech plant industry'.¹⁷²

In Europe, this 'disruption' culminated with the EPO Enlarged Board of Appeal (EBA) decisions on the consolidated referrals G2/12 ('Tomato II') and G2/13 ('Broccoli II'). Considering the stipulations in Article 53 (b) EPC, the EBA affirmed that products, namely plants or parts thereof, obtained by essentially biological processes are in principle patentable under the EPC. This outcome leaves considerable leeway for patenting novel and inventive plants and products thereof which have been produced by 'conventional' methods including breeding steps. The EBA also clarified that this applies irrespective of whether such claims are formulated in product-by-process formats or as per se products. Moreover, the combined effect of *Broccoli/Tomato I & II* opens new opportunities for patenting GMOs. Although major industry players had challenged the relevant patent claims, these were generally good news for innovative plant breeders and agrochemical companies.¹⁷³

¹⁶⁶ Michael A. Kock & Christine Gould, *Adapting IP to an Evolving Agricultural Innovation Landscape*, 2 WIPO MAGAZINE (2013).

¹⁶⁷ *Id.*

¹⁶⁸ *Id.*

¹⁶⁹ Ylva Skoglösa & Isabel Cantalops Fiol, *Do Patents Get in the Way of Feeding the World?*, MANAGING INTELLECTUAL PROPERTY (2016), http://www.valea.eu/sites/www.valea.se/files/field_page_attachments/54-59_valea_europe16.pdf (last accessed May 8, 2017).

¹⁷⁰ Kock & Gould, *supra* note 166.

¹⁷¹ Skoglösa & Fiol, *supra* note 169.

¹⁷² *Id.*

¹⁷³ Minssen & Nordberg, *supra* note 18, at 81–98.

These developments in European patent case law in recent years appear to have widened the divide between breeders and the biotech industry. Under current EPO case law, it appears possible that plant breeders are prevented from using genetically manipulated variants to innovate their breeds without permission from patent holders. This decision has thus been perceived as favoring the big agrochemical corporations to the detriment of small plant breeders.¹⁷⁴ The situation is complicated by the fact that the national patent legislation of some European countries, such as Germany and The Netherlands, explicitly excludes from patentability products produced by essentially biological processes, as well as the processes themselves. Consequently, two European countries with a considerable bioagro industry are clearly not in line with the EPO's *Broccoli II* & *Tomato II* decisions and would probably not have granted those patents.¹⁷⁵ Potential litigation in these countries directed to corresponding or similar types of patent might thus reach the CJEU. This court is not bound by the EBA's decisions and might interpret the Biotechnology Directive in line with German and Dutch implementation. However, EBA decisions may have a more substantial impact at the UPC, once it is finally up and running in Europe.¹⁷⁶ On November 3, 2016, the European Commission adopted a notice on the interpretation of the Biotechnology Directive.¹⁷⁷ Its view is that according to the intentions of the legislator, plants produced by crossing and selection should not be patentable. The effect of the notice on the practice of the EPO, and hence its value for legal interpretation purposes, including possible follow-up measures, is currently under discussion between the EPO and its member states. Faced with pressure from the EU, in December 2016, the EPO decided that 'all proceedings before EPO examining and opposition divisions in which the decision depends entirely on the patentability of a plant or animal obtained by an essentially biological process will be stayed ex officio'.¹⁷⁸ Following internal debates, the EPO Administrative Council decided to amend the relevant implementing regulations in order to exclude from patentability plants and animals exclusively obtained by an essentially biological breeding process. The EPO's proposal adopted by its Administrative Council was intended to safeguard uniformity in harmonized European patent law and perhaps anticipating the possibility and need for national courts to issue further referrals to the CJEU and its potential for legal certainty disruption. The new provisions became applicable with immediate effect starting on July 1, 2017.¹⁷⁹

IV.C.d. Patent Wars: the Battle of Priority and the Battle of the Claims

The CRISPR/Cas9 patent war ignited in Europe with the filing of several oppositions against what is considered to be the first patent granted in Europe for this technology.¹⁸⁰ The patent was granted by the EPO to the Broad Institute, MIT and Harvard

¹⁷⁴ Skoglösa & Fiol, *supra* note 169.

¹⁷⁵ *Id.* See also Minssen & Nordberg, *supra* note 18, at 92–98.

¹⁷⁶ *Id.*

¹⁷⁷ Commission Notice on certain articles of Directive 98/44/EC of the European Parliament and of the Council on the legal protection of biotechnological inventions, C/2016/6997, OJ C 411, 8.11.2016, at 3–14.

¹⁷⁸ Notice from the European Patent Office of Nov. 24, 2016 concerning the staying of proceedings due to the Commission Notice on certain articles of Directive 98/44/EC of the European Parliament and of the Council of July 6, 1998 on the legal protection of biotechnological inventions, OJEP 2016 A104.

¹⁷⁹ Amended rule 27 b), EPC implementing regulations.

¹⁸⁰ EP2771468, granted on Feb. 11, 2015.

College on February 11, 2015, comprising a total of 53 product claims.¹⁸¹ It pertains to research conducted by Feng Zhang and his research group (hereinafter, *Zhang et al.*). It has been opposed by nine different entities.¹⁸² Opposition procedures could result in several different outcomes ranging from amendment of claims to complete revocation of the patent. In any event, it is likely that appeal(s) will be lodged. This can be a lengthy procedure pending several years until a final decision is issued.

The patent landscape is vast and complex. The grant of the *Zhang et al.* patent was closely followed by several divisional European patent applications. Some have been granted,¹⁸³ some are being opposed or are within the nine-month opposition period,¹⁸⁴ while others are under examination.¹⁸⁵ It seems predictable that some of these patents will also be opposed by multiple parties. In the USA, the same patent family already includes at least 13 patents, the first of which was granted on April 15, 2014.¹⁸⁶ Several further European and US pending applications are in this patent family.

A competing patent family directed to CRISPR/Cas9 currently includes a European patent application¹⁸⁷ and a US patent application¹⁸⁸ filed by the University of California, the University of Vienna, and Emmanuelle Charpentier. It covers research conducted by Jennifer Doudna and Emmanuelle Charpentier's teams (hereinafter, *Doudna et al.*). This patent claims a priority date of May 25, 2012, more than 6 months before the priority date claimed in the *Zhang et al.* patent (December 12, 2012).

The subject matter of a patent application must be novel and inventive over all public disclosures made before the priority date. Generally, this also means that if the priority date of *Doudna et al.* is recognized and the corresponding patent granted/maintained, the *Zhang et al.* patent will either be invalidated or remain dependable.

However, while the *Doudna et al.* patent claims an earlier priority date, none of the applications were published until after the priority date claimed by the *Zhang et al.* patents. In Europe, in light of the EPC, this means that the *Doudna et al.* disclosure will only be relevant to the assessment of novelty, but not to the determination of whether the *Zhang et al.* patents involve an inventive step. Considering that details of the CRISPR/Cas9 system were published¹⁸⁹ before the priority date of the *Zhang et al.* patents, in order for the claims of those patents to be patentable they must define subject matter that is novel and inventive over that publication. Opposition procedures consider in this respect whether it would have been obvious, based on the disclosure

¹⁸¹ *Id.*

¹⁸² Communication of notices of opposition, Ref. TBI-2771468-OPP, Patent n. EP2771468, dated Dec. 22, 2015, <https://register.epo.org/application?number=EP13818570&lng=en&tab=doclist> (last visited May 5, 2017).

¹⁸³ EP2784162, granted on Apr. 8, 2015. Also subject to oppositions.

¹⁸⁴ EP2896 697, granted on Sept. 2, 2015; EP2940140; EP2921557; EP2848690; EP2825654.

¹⁸⁵ A patent family search at the EPO lists a total of 194 entries globally. See European Patent Office, Family list: EP2771468(A1) - 2014-09-03, http://worldwide.espacenet.com/publicationDetails/inpadocPatentFamily?CC=EP&NR=2771468A1&KC=A1&FT=D&ND=3&date=20140903&DB=worldwide.espacenet.com&locale=en_EP (last accessed May 24, 2017).

¹⁸⁶ US 8 697 359, granted on Apr. 2014 'CRISPR-Cas systems and methods for altering expression of gene products'.

¹⁸⁷ European Patent App. No. 13793997 'Methods and compositions for RNA-directed target DNA modification and for RNA-directed modulation of transcription'.

¹⁸⁸ US Patent App. No. 13/842859.

¹⁸⁹ Jinek et al., *supra* note 22.

presented by the Jinek *et al.* paper,¹⁹⁰ that the CRISPR/Cas9 system would work in vivo in eukaryotic cells.¹⁹¹

In the USA, because the Doudna *et al.* patent application was filed with a priority date of May 25, 2012—one day before the first-to-file rules in the America Inventor's Act came into effect—a patent interference proceeding was still possible. An *interference proceeding* was initiated listing Doudna *et al.* as the senior party,¹⁹² leaving Zhang *et al.* with the burden of proof. The interference declaration concerned all claims, and the Patent Trial and Appeal Board concluded that the parties claim distinct subject matter, and entered a 'judgment of no interference-in-fact, which neither cancels nor finally refuses either parties' claims'.¹⁹³

In Europe, in March 2017 the EPO announced its intention to grant the corresponding Doudna *et al.* patent.¹⁹⁴ The claims are quite broad and the patent is likely to be opposed.

CRISPR/Cas9 has a complex and undefined patent landscape with possibly several overlapping patent rights. It includes patents and patent applications covering the basic CRISPR/Cas9 system and methods for its use, but also new developments or improvements (eg the new nuclease Cpf1,¹⁹⁵ and specific applications for its use, eg claims for therapeutic uses). In addition to the two competing research groups resulting in the aforementioned patents, other parties are active with patents and patent applications relevant to the technology. Given the number of research teams working in the area, the complexity of the patent landscape is likely to increase with time and generate further patent disputes. For example, the USPTO granted a patent that claims gene inactivation by the use of chimeric restriction endonucleases. This was issued on October 4, 2016 with a priority date of February 3, 1999. The patent owners are the Pasteur Institute and the Boston Children's Hospital, and the inventors André Choulika and Richard Mulligan.¹⁹⁶ Collectis (the exclusive licensee) publicly announced 'an umbrella patent' that 'covers most of the gene-editing procedures done with a nuclease', including those based on CRISPR/Cas9, TALENs, zinc fingers, and many

¹⁹⁰ *Id.*

¹⁹¹ See James Legg, *CRISPR/Cas Patent Wars Have Begun at the European Patent Office*, BIONEWS (2015), http://www.bionews.org.uk/page_589337.asp (last accessed Mar. 10, 2017); See also Jacob Sherkow, *CRISPR Dispute to Be Decided by Patent Office*, MIT TECHNOL. REV. (2016), <http://www.technologyreview.com/view/545411/crispr-dispute-to-be-decided-by-patent-office> (last accessed Mar. 10, 2017).

¹⁹² See Initial interference memo, Dec. 21, 2015.

¹⁹³ Patent Interference No. 106,048, Judgment 37 C.F.R. § 41.127(a), Feb. 15, 2017.

¹⁹⁴ EP2800811 *Methods and Compositions for RNA-Directed Target DNA Modification and for RNA-Directed Modulation of Transcription*. See also Sharon Begley, *University of California's CRISPR Patent Win in Europe Likely to Be Challenged*, <https://www.statnews.com/2017/03/28/crispr-university-of-california-patent/> (last accessed Apr. 18, 2017).

¹⁹⁵ Bernd Zetsche *et al.*, *Cpf1 Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*, 163 CELL 759–71 (2015).

¹⁹⁶ U.S. patent 8,921,332 'Chromosomal modification involving the induction of double-stranded DNA cleavage and homologous recombination at the cleavage site' issued on Dec. 30, 2014; and U.S. patent 9,458,439 'Chromosomal modification involving the induction of double-stranded DNA cleavage and homologous recombination at the cleavage site', issued on Oct. 4, 2016.

meganucleases. Commentators have cast doubt on the patent's validity and scope, an indication that litigation might follow suit.¹⁹⁷

The CRISPR/Cas9 *patent wars* will likely continue over the coming years. Long and complex proceedings, in both the USA and Europe, will unveil who owns the technology and to what extent. Independently of the outcome in the *priority battle(s)*, different players will also seek to oppose and/or partially or totally invalidate specific claims. Different grounds for invalidation are possible, including arguments concerning patent exclusions under the EPC. The outcome of the *battle of the claims* has many variables and is difficult to predict. In the meantime, while the actual ownership status over the technology is undefined and despite ethical controversies, license agreements and joint ventures with major industry partners have been announced. The industry is moving toward future commercial applications, while the public debate on ownership and scientific attribution is somehow overshadowing ethical and regulatory discussions.

In light of this uncertainty, it is not surprising that different forms of intervention are currently being considered in Europe ranging from legislative changes in the EU Biotech Directive, patent law, and procedure to the introduction of special compulsory licensing regimes¹⁹⁸ and creative user-generated and integrated solutions, such as the development of industry wide e-licensing platforms.¹⁹⁹

Whereas a detailed discussion of all possible forms of intervention falls outside the scope of this paper, we will in the following elaborate on these types of solution that seek to *balance the application and governance of IPRs* in relation to upstream and downstream technology.²⁰⁰

IV.C.e. Cross Licensing and Governance

Instead of seeking solutions by modifying the legal framework, some authors have suggested experimenting with private ordering mechanisms generated by users (i.e. patent pools, clearing houses, commons, open source)²⁰¹ to respond to some of the IP-related challenges in synthetic biology and gene editing explained above. These private ordering mechanisms operate within the current legal framework, appear mostly post-grant, and are typically contract-based. They are presumably more appropriate than state-enacted law because normally users would better understand the demands of the sector and they would be able to respond more quickly to those demands without the delay generally encountered in democratic decision-making processes. Moreover, these challenges are international in nature and, hence, any solutions should preferably be international as well. Nonetheless, international negotiations aimed at adoption of a new

¹⁹⁷ See Jon Cohen, *Dramatic Twists Could Upend Patent Battle Over CRISPR Genome-Editing Method*, SCIENCE (Oct. 5, 2016, Updated, 10/7/2016), doi:10.1126/science.aah7381.

¹⁹⁸ See eg Final Report of the Expert Group on the development and implications of patent law in the field of biotechnology and genetic engineering (E02973), published on May 17, 2016, <http://ec.europa.eu/DocsRoom/documents/18604/attachments/1/translations/> (last accessed Jan. 10, 2017) (recommending that no further action be taken).

¹⁹⁹ See eg Kock & Gould, *supra* note 166 (considering contract-based, user-generated solutions, and presenting Syngenta's TraitAbility e-licensing platform).

²⁰⁰ Nari Lee, Soili Nystén-Haarala & Laura Huhtilainen, *Interfacing Intellectual Property Rights and Open Innovation*, SSRN ELECTRONIC J., <http://ssrn.com/abstract=1674365> (last accessed May 8, 2017); Carl Mair, *Openness, Intellectual Property and Standardization in the European ICT Sector*, 2 IP THEORY 3 (2012); Michiel Verlinden, Timo Minssen & Isabelle Huys, *Reconciling IPRs and Openness in Biobanking*, 38 EIPR 1–4 (2016).

²⁰¹ THOMAS RIIS, *USER GENERATED LAW* (forthcoming).

treaty or treaty modifications tend to meet even more hurdles and delays than does state-enacted law, rendering private ordering mechanisms an interesting channel for responding to speedy science-based developments in synthetic biology and gene editing. In this light, the participants at a workshop with experts and stakeholders in November 2013 in Copenhagen sponsored by the European Research Area Network in Synthetic Biology (ERASynBio) recommended (amongst other things) to ‘[e]xplore opportunities for private ordering mechanisms to improve transparency of ownership and to facilitate licensing’.²⁰² Additionally, other authors have signaled the relevance of such models in synthetic biology and gene editing.²⁰³

Different types of private ordering mechanisms exist, ranging from IP sharing and *freedom to operate* models, such as SYNGENTA’s e-licensing platforms²⁰⁴ or LEO PHARMA’s open innovation platform²⁰⁵, to industry-wide licensing platforms.²⁰⁶ This position might also embrace the idea that upstream or basic technology should be kept free of inhibiting IP, while downstream technology and products may be subject to IP. This seems to be the approach of the BioBricks foundation, a key player in efforts to create a freely accessible repository of standardized biological parts. The agreement that governs the terms of contribution and use of BioBricks seeks to ensure that basic bioparts are not covered by IPRs or that the owner of IPRs agrees to non-assertion. However, the agreement contains no clauses that prevent products that may be constructed from the combination and assembly of the parts from being patented or otherwise protected by IP.²⁰⁷

With regard to gene-editing technology, patent pool or clearing house models (or combinations of the two models) could be especially helpful in dealing with IP fragmentation. Inspiration for such approaches could be gathered from the ICT sector. This was demonstrated in December 2016, when MPEG LA, one of the main operators of one-stop licenses for standards and other technology platforms in consumer electronics, announced that it has begun to examine the CRISPR-cas9 patent landscape to identify essential patents that would need to be bundled together in licensing pools to enable a

²⁰² Timo Minssen, Berthold Rutz & Esther van Zimmeren, *Synthetic Biology and Intellectual Property Rights: Six Recommendations—Report from the IP Expert Meeting at the Danish Agency for Science, Technology & Innovation*, 10 BIOTECHNOL. J. 236–41 (2015).

²⁰³ Arti Rai & James Boyle, *Synthetic Biology: Caught between Property Rights, the Public Domain, and the Commons*, 5 PLoS BIOL. e58 (2007); Berthold Rutz, *Synthetic Biology and Patents. A European Perspective*, 10 EMBO REP. S14–17 (2009).

²⁰⁴ The first initiative, the Syngenta e-licensing platform, TraitAbility, makes available some of the company’s most important native trait technology and a range of research tools for biotechnology, see <http://www3.syngenta.com/global/e-licensing/en/e-licensing/Pages/home.aspx> (last accessed Jan. 10, 2016).

²⁰⁵ LEO Pharma Open Innovation is a collaborative space created to explore partnerships and collaborate using disease-relevant in vitro assays as an initial stepping stone. The open innovation platform allows insight and access to some unique research tools in order to test external compounds for disease-relevant effects, but without the Partner having to disclose confidential information or giving up IP, see <http://openinnovation.leo-pharma.com/> (last accessed Feb. 15, 2016).

²⁰⁶ Kock & Gould, *supra* note 166.

²⁰⁷ Cf. *The BioBrick Public Agreement (BPA)*, Biobricks Foundation, <https://biobricks.org/bpa/> (last accessed Feb. 19, 2016).

one-stop license ‘platform to reduce litigation risk and provide efficiency, transparency and predictability to scientists and businesses worldwide.’²⁰⁸

IV.D. Legal System Coherence

There is a considerable legal theoretical, but also political, discussion concerning policy options between pluralism and harmonization. The discussion emerges concerning every negotiation of an instrument of international law. Internally it is often present in debates concerning the limits and boundaries of federal legislative powers, or centralization versus regionalisation. It is also particular visible in political debates concerning plurinational integration projects such as the EU. Emerging technology, such as gene editing, presents a multitude of horizontal challenges across a variety of legal disciplines. It is also a technology which raises deep social and ethical questions and as such entails possibilities for further legal and regulatory overlaps. As demonstrated in this section, gene editing opens interpretative and even legislative challenges because often it is not clear how these new technologic realities fit into legal categories, and operative concepts of the applicable rules and regulations.²⁰⁹

The existence of a multi layered framework of laws and regulations is simultaneously cause and consequence of a complex network of legal overlaps. As mentioned above, patentability exceptions or eligibility standards play a public policy role akin to technology regulatory norms. Although these are independent from technology regulations, intersections should be considered and the need or not for coherence addressed, in particular, coherence between legal interpretation of patent exceptions to gene-editing processes and the regulatory framework applicable to such intervention. Because the regulatory framework might distinguish between different technological applications, interpreting eligibility rules as intended to deny incentives to research that seeks to eradicate the transmission of severe hereditary diseases to future generations is at odds with the function of the patent system. As a matter of legal interpretation, it has to be investigated in light of the intention and purpose of the patent system whether the legislator would have allowed for a broader patent eligibility approach if it had anticipated the technological possibilities for therapeutic applications provided by gene-editing technology.

The issue of dual use is of particular importance to the concrete determination of whether a technology should be excluded from public incentive mechanisms.²¹⁰ Certain gene-editing intervention is or will be prohibited based on a number of reasons (public health, precaution and safety concerns, or human dignity), while less controversial applications might be allowed. However, patent protection is not necessarily

²⁰⁸ MPEG LA, MPEG LA Initiative to Address CRISPR Licensing, *One-Stop Access Will Accelerate Advances in New Medicines, Organ Transplants and Agriculture* (2016), <http://www.businesswire.com/news/home/20161206006182/en/MPEG-LA-Initiative-Address-CRISPR-Licensing> (last accessed May 17, 2017).

²⁰⁹ See Ana Nordberg, *Legal Method and Legal Interpretation in International IP Law: Pluralism or Systemic Coherence*, in ATRIP CONGRESS 2016 PROCEEDINGS INTELLECTUAL PROPERTY AS FUNCTIONAL PLURALISM: THE PARAMETERS, CHALLENGES AND OPPORTUNITIES OF VARIATION (Suzy Frankel ed., Edgar Elgar, forthcoming) https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3035771.

²¹⁰ See section 4.2.

purpose-bound, so that only in certain claim types (eg secondary uses) would it be possible to differentiate. When a given invention can be developed in different directions, it is excessive to deny patentability and thus incentives to innovation.

Moreover, legal coherence will imply that similar public policy considerations will have to apply *mutatis mutandis* to other public forms of incentive, such as research grants, prizes, and awards. Likewise, cross-license mechanisms and contractual arrangements should equally be developed in light of general legal principles. Finally, gene editing is simple to use in non-institutional contexts. Incentives to further research and innovation are a powerful tool to stir technology in a socially responsible and safe direction, but the nature of the technology implies the need for additional mechanisms of governance such as exploring the possibilities for multilevel stakeholder dialog and private society engagement.

Law, in its broader sense, is created, and developed in a given social context. Narratives on science and technology play an interesting role on defining how different actors will apply, interpret, and use their agency or discretionary powers. Court adjudication, institutional practice by patent offices, decisions by ethical boards and regulatory approval authorities, negotiation of contractual arrangements and business strategies, and even individual decisions by private actors are not made in the vacuum, but rather inserted in a social context. In the next section, we address both the role and influence of communication and public perception in legal debates concerning the regulation of emerging technology, and on the other side the influence of litigation in the construction of such narratives.

V. COMMUNICATION AND PUBLIC PERCEPTION

The technological ability to alter genes has for a long time been a controversial issue in public debate. In 1975, the Asilomar conference²¹¹ crystallized public attention on the risks and merits of recombinant DNA technology, but controversies about genetic inheritance go much further back (for instance around the use of eugenics). During the 1970s and 1980s, however, controversies over the use of genetic modification in agriculture and human and animal reproduction regularly surfaced in many countries around the world. In the 1990s, these debates reached unprecedented public attention with the decision to mix GMO and non-GMO soybeans in American exports to Europe in 1996, and the birth of the cloned sheep Dolly in 1997. These developments resulted in what has been called a ‘global controversy on biotechnology’.²¹²

In many ways, current public debate about gene editing is therefore building on, or reviving, controversies and arguments which are already deeply entrenched in many societies. At the same time, the tendency is to present the issues as revolutionary and as if this specific point in time is more crucial than any other. This was also the case when the US National Academy of Science, the US National Academy of Medicine, the Royal Society, and the Chinese Academy of Sciences hosted an international summit on Gene Editing in Washington, in December 2015 (the organizers later referring to

²¹¹ Priska Gisler & Monika Kurath, *Paradise Lost? ‘Science’ and ‘the Public’ after Asilomar*, 36 SCIENCE TECHNOL. & HUM. VALUES 213–43 (2011).

²¹² MARTIN BAUER & GEORGE GASKELL, *BIOTECHNOLOGY: THE MAKING OF A GLOBAL CONTROVERSY* (2002).

this as the Human Gene Editing Initiative (HGEI)²¹³). The Chairman of the organizing committee, David Baltimore, laid it out in the introduction:

Today, we sense that we are close to being able to alter human heredity. Now we must face the questions that arise. How, if at all, do we as a society want to use this capability? This is the question that has motivated this meeting.²¹⁴

What such statements make clear is that more is at stake than simply a technology or a technological platform. It is about how society develops and how various groups of stakeholders, governments, and publics try to direct this development. Such an understanding of controversies as deep-founded disagreements about values is also in line with much of the scholarly research on public controversies about biotechnology which have been published during recent decades.²¹⁵ That research forms the background for this section.

One of the crucial points of discussion at the 1975 Asilomar conference was whether science's system of self-regulation is trustworthy and robust, or whether it is necessary to enforce regulation from the outside. Several decades later, when the debate about GMO had developed into a full-scale global controversy, this was still a key issue for publics around the world: Can we trust science to govern its own development in a socially acceptable way? In a seminal analysis of the use of biotechnology in the health care system, Michael Mulkey has shown that most of the argumentation on either side of the controversy springs from a basic assessment of the role of science in society.

That is to say, while proponents see science as a positive force in society, which brings about solutions to problems, and present this worldview in a rhetoric of hope, opponents understand science to be a social phenomenon which creates more problems than it solves and present this worldview in a rhetoric of fear. Interestingly, both sets of arguments present technoscientific solutions as revolutionary and as having far-reaching consequences. In this context, the important point is that any new technoscientific development will be seen in light of previous controversies.

When public communicators (for instance journalists and opinion makers) make sense of a new phenomenon, they will invariably draw a comparison with known examples and use these frames of reference to make sense of new developments by presenting them in well-known storylines. What this part of history also reminds us is that the call for a moratorium on human germline editing by the Washington meeting in 2015 has a clear precedent in the 1975 Asilomar conference—a call, however, whose current efficacy can be very hard to evaluate. While its regulatory impact is probably quite small—as dealt with elsewhere in this paper—its public value in terms of generating legitimacy might be more important. By calling for a moratorium on the use of certain aspects of CRISPR/Cas9 technology, other aspects of use can simultaneously be treated as legitimate and justified.

²¹³ See The National Academies of Sciences Engineering Medicine, *Human Gene-Editing Initiative* (2017), <http://www.nationalacademies.org/gene-editing/index.htm> (last accessed Mar. 3, 2017).

²¹⁴ *International Summit on Human Gene Editing: A Global Discussion* (2017), <http://www.nap.edu/21913> (last accessed May 17, 2017).

²¹⁵ In 1992, the journal 'Public Understanding of Science' was started and has since been one of the hotspots of research on public controversies over science, but there are a number of earlier studies, see eg DOROTHY NELKIN, *CONTRIVERSY: POLITICS OF TECHNICAL DECISIONS* (1st ed., 1979).

V.A. Science and Society

After the Washington meeting, the HGEI commissioned a ‘consensus study’ of ‘the scientific underpinnings of human gene-editing technology, its potential use in biomedical research and medicine—including human germline editing—and the clinical, ethical, legal, and social implications of their use’.²¹⁶ The aim of this study was formulated by the actors behind the HGEI in a concluding statement after the original Washington Meeting: ‘The forum will mobilize the global expertise necessary to help society develop norms for acceptable uses of human gene-editing technology. This is an important moment in human history and we have a responsibility to provide all sections of society with an informed basis for making decisions about this technology, especially for uses that would affect generations to come’.²¹⁷

While this is certainly a noble ambition, social scientific research into public controversies about emerging technology suggests that such an approach might not be successful. It might not be so easy to ‘help society develop norms for acceptable uses’, just as the idea of ‘providing society with an informed basis for decision-making’ is in danger of misinterpreting the fundamental drivers of the controversy. In this context, we will just mention two reasons for this.

First, science and society should not be regarded as two distinct spheres, such that science can be developed independently of social, ethical, and legal reflection and only subsequently be made the object of societal decision-making. Rather, science is part of society, and social sense-making about it is a continuous process. It is therefore utterly problematic to first do the science and subsequently agree on the norms for its uses. Science does not take place in a vacuum, but in a society in which a myriad of actors have interests and want to influence or oversee its activities, applications, and implications. One good example of this can be found in the pre-history of CRISPR/Cas9 technology. Interestingly, the experimental evidence for the CRISPR/Cas9 system was first obtained at the sugar and food ingredients company *Danisco*.²¹⁸ During the 1980s, they also developed sugar beet resistant to glyphosate through the use of genetic engineering. In an effort to take into consideration the criticism of using antibiotic resistance genes as a selection marker, a new selection system based on sugar mannose was implemented. These innovations were, however, never commercialized by *Danisco* due to environmental concerns. In light of general European skepticism toward the use of GMOs in agriculture, *Danisco* decided to discontinue its R&D activities in this area. This story demonstrates how a corporation tried to be responsive to public concerns (over the use of antibiotic resistance genes), but ended up halting its otherwise promising path of technology development because of concerns over public skepticism toward GMO crops. *Danisco* was not the only European company to put a halt to agricultural biotechnology around the turn of the century. Indeed, in many ways public skepticism toward GMO has become a seminal lesson about the need to take public concerns seriously in order

²¹⁶ The National Academies of Sciences Engineering Medicine, *Human Gene-editing Initiative*, <http://www.nationalacademies.org/gene-editing/consensus-study/index.htm> (last accessed Mar. 3, 2017).

²¹⁷ *International Summit on Human Gene Editing: A Global Discussion*, *supra* note 214.

²¹⁸ Researchers at the company discovered that the thermophilic Gram-positive bacterium *Streptococcus thermophilus* was resistant to virus attack when harbouring the CRISPR/Ca9s system and that the specificity of the resistance was determined by the variable spacer sequences of the CRISPR locus and their sequence homology to the protospacer sequence in the viral genome.

to avoid them later on preventing technological development.²¹⁹ Avoiding the GMO trap is seen to be paramount.²²⁰

While it is certainly important to provide material that will help societal actors deal with the social, ethical, economic, technical, and political challenges posed by the development of gene-editing technology, it is not plausible to imagine an orderly linear process of information gathering, development of norms, decisions about acceptable applications, and subsequent dissemination of technology. Rather, these things happen at the same time and in many conflicting and interrelated processes. Just to mention one example, the patent dispute demonstrates how economic expectations are already enormously important in shaping the framework for gene-editing technology. In such situations, all communication about the technology can be seen to be directed by vested interests. One clearcut example of this is the January 2017 piece by the Director of the Broad Institute, *Eric S Lander*, in *Cell*, entitled ‘The Heroes of CRISPR’.²²¹ This piece was heavily criticized for demonstrating typical sexism in science by downplaying the role of female scientists *Jennifer Doudna* and *Emmanuelle Charpentier* with obvious links to the story of *Rosalind Franklin* and the Nobel prize for the discovery of DNA. However, such story writing has also undoubtedly importance in terms of influencing public perceptions of the ongoing patent trial. If *Lander* had been successful in describing *Doudna* and *Charpentier* as only some among several scientists working with CRISPR, and portraying *Zhang* as the central hero, he would have strengthened the claims by *Zhang* and therewith those of the *Broad Institute*. As it happens, however, the social media storm that arose around *Lander*’s article might well have had adverse effects on their cause. The point here is that science is not separate from the rest of society but intermingled with many different parts of society and a myriad of actors will take an interest in what happens within science. Communication about science is therefore not something that can happen ‘after the fact’ of its development.²²² Rather, communication forms part of making scientific and technological development happen.

Second, and linked to the first aspect, we need to be aware of the fundamental unease in the relationship between science and democracy in our democratic societies. On the one hand, science, as any other aspect of society, should be democratically accountable. On the other hand, however, this accountability challenges the epistemic authority of science and its accountability toward truth. Philosophy of science has produced a number of suggestions for how to deal with this challenge, but the basic tension remains: Can we democratically decide on what should count as truth in society? The idea of a ‘consensus study’ as formulated by the HGEI builds on the idea that a group can identify the areas and arguments upon which there is consensus—which suggests that truth and democratic decision-making are aligned, thereby circumventing potential tensions between science and politics. However, the HGEI followed up by suggesting that all aspects of society should be provided with an ‘informed basis for making decisions’,

²¹⁹ Elise McCarthy & Christopher Kelty, *Responsibility and Nanotechnology*, 40 SOC. STUD. SCI. 405–32 (2010); Nick Pidgeon & Tee Rogers-Hayden, *Opening Up Nanotechnology Dialogue with the Publics: Risk Communication or ‘Upstream Engagement’?*, 9 HEALTH RISK & SOC. 191–210 (2007).

²²⁰ Arie Rip, *Folk Theories of Nanotechnologists*, 15 SCI. CULTURE 349–65 (2006).

²²¹ Eric S. Lander, *The Heroes of CRISPR*, 164 CELL 18–28 (2016).

²²² Ursula Plesner & Maja Horst, *Before Stabilization: Understanding the Communicative Aspect of Non-standardization of 3D Digital Models in the Building Industry*, 16 INFO. COMM. & SOC. 1115–38 (2017).

thereby bringing those tensions back into play. During the first decades of controversy over biotechnology, the most common explanation of opponents' skepticism was that they lacked information or knowledge about the technology—and as soon as they became informed they would cease to be skeptical. An overwhelming number of studies have demonstrated that this explanation is too simplistic and/or simply wrong.²²³ Many skeptics are well informed about the technology in question, but evaluate and value specific facts, risks, and insecurities differently from supporters of the same technology. Similarly, the notion of an 'informed basis for making decisions' needs to be unpacked, so that it takes into account that the question of what counts as knowledge and information is often a controversial issue in itself.²²⁴

V.B. Public Trust

As mentioned above, a fundamental aspect of controversy about biotechnology can be understood as a question of whether actors see science as a solution to problems in society or whether science is seen as something that creates problems. At the core of this discussion lies the issue of trust (linked to questions of control, blame, and social integration, but for reasons of simplicity we focus on trust here²²⁵). If people are to be convinced by arguments built on information and knowledge, they have to trust the credibility and ethos of the speaker. A fundamental problem for proponents of gene editing is therefore to establish science as a credible source of true and/or useful knowledge and beneficial technology. As long as large parts of societies do not believe that technoscientific development can be trusted to be in the interest of improving society—including those disbelievers—then skepticism toward the technology will prevail. Rather than talking about establishing an informed basis for decision making, the main focus should therefore be on establishing trust.²²⁶ However, in this regard, patent trials risk making this effort much harder. Studies of public trust in science demonstrate that while many people are sympathetic to the idea of science in itself—as an activity for establishing true knowledge—they become deeply skeptical when science is seen to be in cahoots with market forces and multinational companies.²²⁷ Patent litigation that drags out for years will therefore in itself most likely contribute to skepticism because it suggests that scientists and scientific organizations are really 'in it for the money' rather than being concerned about truth and improving people's lives.

Despite these complexities, we do not mean to suggest that the HGEI has no merit. The crucial question is what our expectations toward public discussion of this technology should be. Public engagement and deliberation is not likely to produce final solutions to controversy about biotechnology. However, this does not mean public discussion is futile—rather, it suggests the opposite. Since public discussion concerns the role of science in shaping future society, it amounts to some of the most important

²²³ MARTIN W BAUER, *ATOMS, BYTES AND GENES* (2015).

²²⁴ ALAN IRWIN & BRIAN WYNNE, *MISUNDERSTANDING SCIENCE?* (1996).

²²⁵ Maja Horst, *Collective Closure?: Public Debate as the Solution to Controversies about Science and Technology*, 53 *ACTA SOCIOLOGICA* 195–211 (2010); MARY DOUGLAS, *RISK AND BLAME—ESSAYS IN CULTURAL THEORY* (1996).

²²⁶ Rick E. Borchelt & Kristian H. Nielsen, *Public Relations in Science: Managing the Trust Portfolio*, in *ROUTLEDGE HANDBOOK OF PUBLIC COMMUNICATION OF SCIENCE AND TECHNOLOGY* 58–69 (Massimiano Bucchi & Brian Trench eds. 2014).

²²⁷ Torben Hviid Nielsen, *Public Perception: Behind the Color Code of 'No'*, 15 *NAT. BIOTECHNOL.* 1320–21 (1997).

political discussion for the future knowledge society. Public discussion offers a possibility of placing science right at the heart of political decision-making in society, and makes crystal clear that the key issue is about trust. However, we need to avoid looking at current skepticism toward gene editing²²⁸ as a nuisance or as a roadblock to be cleared as fast as possible. Rather, it is an opportunity for a much more fundamental discussion of the role of science in society and for establishing a better and more trustful relationship between science and other parts of society. While this approach is not made easier by the patent disputes over CRISPR/cas9, scientists and other actors who want to support technoscientific progress in society have to find ways of engaging in fruitful dialog and discussion with the rest of society. Such engagement should not be restricted to technical aspects of gene editing, but has to encompass the overall role of science in society, and the use and merits of scientific methods in a way which includes actors, rather than leaving them outside or—even worse—disenfranchised or alienated. The fact that science ultimately has to be democratically accountable does not mean that scientists have to simply succumb to whatever is democratically decided in society, but that they have a duty and an obligation to participate in democratic decision-making and to make sure that the resulting technoscience is evaluated as democratically robust and acceptable. This work is importantly not about selling science to the public, but about a lively democratic discussion, in which all parties enlighten themselves and each other about how to create a robust knowledge society.

VI. A WAY FORWARD

The broad implications of gene-editing technology and the wide spectrum of potential misuses have to be clearly addressed. Simultaneously, science and scientific freedom is an essential human value that must be preserved and defended. In that regard, it can be assumed that blanket bans on some applications of gene editing are inefficient if they are not internationally enforceable. Theoretical research will proceed and experimentation is likely to relocate to more permissive jurisdictions.²²⁹ Moreover, the danger is that moratoria will merely postpone the problem until an actor with overwhelming market power steps in, sweeping aside regulatory approaches and flipping the power balance by building and using market demand to pressure for favorable regulations.

This means that upfront embedding of ethical, legal, and communication considerations in bioscience research is necessary. Freedom to pursue new avenues to advance knowledge and technical possibilities should entail special attention to risk assessment, prevention, and management. Funding for these areas should be a top priority in the gene-editing area.

A Bio-Law framework is already established in International, European, and National legislation. This framework is based on a notion of human genes as humanity's common heritage. However, this legal concept and its linkage with human dignity should not be interpreted literally. International texts clearly defend diversity and state

²²⁸ Cary Funk, Brian Kennedy B & Elizabeth P. Sciupac, *U.S. Public Opinion on the Future Use of Gene Editing*, U.S. PUBLIC WARY OF BIOMEDICAL TECHNOLOGIES TO 'ENHANCE HUMAN ABILITIES' (2016), <http://www.pewinternet.org/2016/07/26/u-s-public-opinion-on-the-future-use-of-gene-editing/> (last accessed Sept. 24, 2016).

²²⁹ Katrine S Bosley et al., *CRISPR Germline Engineering—The Community Speaks*, 33 NAT. BIOTECHNOL. 478–86 (2015).

that heritable genetics are only a part of what human beings are, as social and cultural elements are also of fundamental importance. These texts also recognize that epigenetic effects are important and that the human species has not ceased to evolve. In the context of gene editing, human dignity should not be understood as equivalent to preserving a legal fiction of static biological identity. A more useful framework will focus on drawing balanced boundaries and establishing guidelines for the exercise of autonomous informed personal choices vis à vis their wider social implications.

Concerning innovations in plants and animals, a regulatory framework for emerging science and technology should take into consideration the broader picture of the global challenges that humanity is facing, such as the responsibility of humanity to maintain and preserve the biosphere and biodiversity, and counteract the effects of human intervention (such as global warming) which in turn are also mentioned in the human rights framework.

Law and regulations should address ethical considerations. In this sense, we conclude that reasonable precaution will remain necessary to address uncertainties but that it should not unnecessarily hold back science. Normative choices should not be prisoners of scientific unknowns. Safety issues of emerging technology for intervention in the human body can be tackled similarly to other health and wellness technology. Individual (and collective) *risk versus benefit* assessment should guide and underline autonomous and informed decisions. General safety rules concerning testing on human subjects, clinical use of experimental procedures, clinical trials, product safety, and environmental protection can adapt to technological progress. In sum, we submit that regulations should be imbued with flexibility while preserving their preventive and precautionary function.

In addition, ethical evaluations of emerging technology, such as gene editing, will increasingly have to address 'dual-use' dilemmas. Gene-editing technology will have a vast number of distinct possible applications, some more controversial than others. Blanket prohibitions and moratoria do not serve the best interests of society. At the current stage, the preferable route rests in specific ethical evaluation at each stage of research and technology use, accompanied by upfront embedding of dedicated research into the ethical, legal, and social implications of the underlying bioscience research.

Although patent law function is mostly anchored in utilitarian arguments, in Europe rules on patentable subject matter and exceptions from patentability assume a de facto public policy role and can be described as entailing *regulatory effects*. Construction of such norms through judicial adjudication reveals a need for a stronger interface between legal arguments, scientific state of the art, and ethical and social considerations.

With regard to intellectual property rights, we believe that the traditional structure for incentivizing technological progress should be neither disregarded nor overused. Improvements in patent examination procedures will bring clarity and avoid upstream litigation. Pre-grant mechanisms can restrict incentives for technology deemed unethical, or lacking novelty or inventiveness. Further clarification on the functioning and application of the research exemption and strengthening user-generated solutions at the post-grant level will mitigate typical limitations on research imposed by patent rights. Given the extremely complex and dense IP landscape in gene editing, it will be particularly important to explore novel ways for governing, managing, and sharing protected

technology through clearing houses and patent pools. MPEG LA's recent initiative to address CRISPR licensing provides an interesting example of such approaches.²³⁰

Emerging technology in life science generally creates heated and emotionally charged debate. In a democratic society, the task of creating new regulations and/or applying existing frameworks to such new technology is not, and should not be, immune to social debate. However, public debate often falls prey to myths and misinformation. In this context, scientific communication should claim a prominent role. Regarding the communication-related aspects of gene editing, we would like to stress that scientific communication should reflect the role of science in society and its essential role for humanity and civilization. Past atrocities should serve as a permanent warning of what must never be repeated. However, this should not cast the shadow of distrust over science. While transparency and accuracy should guide scientific communication, global-scale responsibility and governance should be fostered by and for every stakeholder. A positive stance toward scientific development should guide interdisciplinary dialog. In that respect, we are convinced that interdisciplinary thinking is crucial and should increasingly form part of future legislative initiatives and other types of legal development. Stakeholders and public engagement in debate are also necessary in order to create a base for legitimacy. And in order to contribute to that way forward, we suggest five general guidelines for each actor's engagement in public discussion of gene-editing technology, as well as for broader discussion of technoscientific development:

First, we believe that communication should focus on building trust and long-term credibility. This can only be achieved when all actors feel that they are respected as valued members of society. It is crucial to address concerns openly and take them seriously. In a world of disinformation, all arguments, no matter how irrational or emotional, should be answered with facts or other forms of reasoned argumentation.

Second, scientists need to become more proactive and visible in communicating their research, since trust has to be built through direct relationships with other actors. Professional communicators are important, but communication cannot be left entirely to marketers and public relations professionals.

Third, communication and public engagement should form an ongoing aspect of technoscientific development, rather than an add-on once some technology is fully developed. Constructive criticism is a resource for development of robust technology. At the same time, ongoing discussion of possibilities, opportunities, and risks also serves to develop, strengthen, and nuance the ability of various publics to understand the complexities of emerging technology.

Fourth, the scientific-technological community should engage in a concerted effort in seeking to prevent public science communication from being taken over and steered by the disputes and arguments of the interested parties in intellectual property litigation. Put differently, too many IP tactical considerations influencing how public science is communicated might result in erosion of general trust in science as an activity with beneficent societal goals.

Finally, normative decisions should, to the greatest possible extent, be based on the state of the art in the sciences (natural and social), ethics, and legal scholarship. This is a complex task, not only due to rapid scientific developments, but also because, since

²³⁰ See *supra* note 208.

gene editing is a global challenge, solutions need—as far as possible—to be debated and established at a global level.

Negotiation of international treaties and enactment of derivative international legislation is a complex, lengthy process. Simultaneously, supranational entities face growing criticism over lack of transparency, lack of accountability, and democratic deficit. Reception and implementation of international instruments faces considerable hurdles resulting in lack of harmonization or deficient implementation. Furthering multi-actor dialog, such as we propose, would also likely result in an improvement in ongoing efforts to develop legitimacy and ensure enhanced compliance with international legislation.

Because international negotiations take time and are often linked with complex international relations strategies and power balances, harmonization through parallel legislative national development is often the only time-efficient solution. In this context, a broader and inclusive debate can bring forth a wider range of informed arguments and achieve at least a minimum degree of international consensus. In light of slow regulatory response, informal and soft law mechanisms can play an important role in achieving an alternative route to regulation, an example are emerging initiatives, debates and calls for major right holders to commit to ethical licensing.²³¹ In this sense, corporate social responsibility could also benefit if the major actors adopt a cross-disciplinary embedding in their research and development and a multilevel framework for dialog in their internal decision making. Furthermore, research funding bodies should consider paying closer attention to IP questions, namely addressing the responsibilities of surrogate licensing entities.

VII. CONCLUDING REMARKS

In this paper, we have argued that the complex issues of regulating emerging technology require an interdisciplinary dialog that should be based on multi-actor approaches. The need for these approaches became particularly evident in our analysis of groundbreaking developments stimulated by gene-editing technology. These raise a variety of pressing scientific, legal, ethical, and societal issues, ranging from regulation of science and protection of inventions to crucial ethical issues and narratives of public perceptions.

The debate is far too important and pervasive to be paralysed by disciplinary feuds and lack of communication. The exceptional nature of the technology and its unprecedented potential presents not only great challenges but also the rare opportunity to develop suitable lines of jurisprudence and adapt laws and regulations. We regard the interdisciplinary approach here proposed as a tool to face known risks and uncertainties, and ensure that the law is neither left lagging behind technological development nor caught up in rhetorical traps. Given the rapid speed of technological developments, the risk arises that overstrict legal and regulatory frameworks result in a straitjacket that could limit technological development. Definitional issues and user-generated solutions pose a particular challenge, not only as a matter of legal interpretation but also as a broader communicational concern. Since the progress of science regularly outpaces legislative creation and judicial adjudication, legal definitions can easily become outdated and hamper innovation. Their enactment must be fully informed and their

²³¹ Jacob S. Sherkow, *Patent Protection for CRISPR: An ELSI Review*, 43 J. L. & BIOSCI. 565, at 571 (2017).

usefulness carefully considered. In areas as dynamic as life sciences, inclusion of dynamic interdisciplinary elements should complement literal and historical elements in traditional legal interpretation. This must be balanced by the need for a certain degree of legal certainty, which will remain important for most stakeholders.

While this paper presents a selection of regulatory issues that we regard as particularly relevant, including the important regulatory effect of patent rules, it is also important to recall that these merely represent the tip of the iceberg. Law is a complex system of norms, additional regulatory frameworks, and other IP rights, such as copyright, data protection, regulatory exclusivities, and trade secrets, which have an increasing impact on innovation in the life sciences. Increasing intersections and overlaps between these laws, rights, and regulations have to be factored into legal analysis through application of a systemic perspective. It also became clear that in order to achieve well-balanced and feasible solutions, it will be absolutely mandatory to carefully distinguish between the great variety of techniques used in gene editing and the completely different areas of applications.

Against this background, we believe that broader societal involvement, public communication, dialog between sciences, interdisciplinarity, and proactive legal thinking and use of contextual interdisciplinary elements in legal interpretation and legislative activity have become more important than ever. It is essential to take a positive stance toward science and technology, a stance that allows us to reap the benefits while solidly anchoring research and market practices in the fundamental values of humanity. The regulatory framework needs to be further developed so as to effectively channel the power of technology and direct it to beneficial applications. Humanity should be kept in the driving seat, rather than being trampled by technology.

ACKNOWLEDGEMENTS

The research for this paper was supported by the BioSYNergy project, under the University of Copenhagen's Excellence Program for Interdisciplinary Research. All authors were affiliated with the Centre for Synthetic Biology, an interdisciplinary centre composed of academics from the Faculties of Law, Science, Health, Medicine, and the Humanities. Prof. Timo Minssen research is also supported by the Collaborative Research Programme in Biomedical Innovation Law at the University of Copenhagen which is funded by the Novo Nordisk Foundation (grant agreement NNF17SA027784). Prof. Timo Minssen research is also supported by the Collaborative Research Programme in Biomedical Innovation Law at the University of Copenhagen which is funded by the Novo Nordisk Foundation (grant agreement NNF17SA027784).